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CONSIDERATIONS IN THE USE OF ULTRAVIOLET RADIATION IN OPERATING ROOMS

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DURING the past decade increasing interest has led to many studies of the various factors which affect wound healing in an effort to reduce the complications which may threaten the patient's life or may prolong the stay in the hospital.

The factor to which greatest attention has been directed is infection, and every effort has been made to determine the various sources of wound contamination. That every wound is contaminated is accepted by nearly every surgeon. By improvements in technic in obliterating dead spaces, minimizing tissue trauma, and preventing hematoma, the contaminating organisms will not find suitable cultural environment, but the length of time required to execute a meticulous technic prolongs the time of exposure of the wound to the various sources of contamination. Among the most important of these are the skin of the patient, the materials and instruments coming in contact with the tissues either directly or indirectly, and the operating personnel who may harbor organisms on their hands, clothing, shoes, and noses and throats. These organisms may fall on the floor, contaminate sterile materials, or be disseminated in the air to fall later on the sterile field.

Twenty-five years ago, Brewer[8] was among the first to conscientiously determine the frequency of operative wound infection. He laid particular stress on scrubbing the hands and advised wearing rubber gloves. In 1926, Meleney[36] emphasized the importance of adequate masking when he identified a hemolytic streptococcus found in a hernia repair wound with a similar organism found in the nose and throat of one of the nurses on the operating team. The necessity for masking both nose and mouth has been emphasized by Davis,[17] Walker,[55] and Waters.[57] Dandy[16] and, more recently, Walter[56] have stressed the importance of the effectiveness of the sterilizing apparatus, autoclaves, instrument sterilizers, *etc.* Tinker,[53] Scott,[49] and others[42] have reported upon their experiences with agents advocated for skin "sterilization." A number of authors have demonstrated the possibility of wound contamination from improperly sterilized suture materials, especially catgut.[11, 37] In

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1935, Meleney[38] reported a nine-year study of operating room technic indicating the importance of closing all of the doors through which contamination may come and showing the advantages of silk over catgut in rendering the wound a less fertile soil for the growth of contaminating organisms, a thesis first held by Kocher[30] and later by Halsted.[22] The philosophy of the "silk technic" has been described by Whipple,[62] in 1933. Complete clinical and experimental evidence was given to show the superiority of silk over catgut in clean wounds, providing that the precautions of its use were observed. Its value was further emphasized in the repair of abdominal wounds[63] where the proper method of employment was given.

In the earliest days of antiseptic surgery, Lister[32] considered the air as a probable source of infection, and carbolic spray was used to kill organisms in the air. It was soon evident, however, that other sources of contamination were equally important and attention was directed toward them. Air as a source of contamination was neglected and Chaplin,[10] in 1914, wrote that a great deal of the theory of air-borne infection was unsupported.

Recently, more serious consideration has been given to the air as an important source of wound contamination. Meleney[38] found that ten times as many colonies developed on plates exposed during an operation as on plates exposed in the same operating room while no operation was being performed. He estimated that between 30,000 and 60,000 viable organisms fell upon the "sterile" field during the course of an hour's operation.

The relationship of wound infection and the patient's postoperative course to the bacteriologic content of the air in operating rooms was shown by Drets and Diago.[18] They found that when the operating team came into the room, the normal air contamination was raised 32 times.

Interest in combating air contamination was stimulated by Wells,[58] in 1934, when he showed that moisture droplets from the nasopharynx do not necessarily fall to the ground, but remain suspended in the air and may be considered responsible for transmission of respiratory disease. The size and viability of the organisms are the important factors. He[59] studied the effect of ultraviolet radiation on certain species of bacteria in the air and found that they could be destroyed. Further studies were made on the viability of air-borne organisms and their relation to communicable diseases which might arise in schools, hospitals, and other public buildings.

The application of ultraviolet radiation for sterilization of air in the operating room was described by Hart,[23] in 1936. He found that the usual precautions of sterile technic did not control infections in wounds of major proportions such as thoracoplastic procedures unless bactericidal ultraviolet generators were employed. He emphasized the employment of ultraviolet radiation, from a source essentially monochromatic, which would have the highest bactericidal and the least erythemal effect. He used a cluster of eight tubes at a distance of five feet from the operating room table. The bactericidal effect was determined on seeded plates and it was found that the intensity was sufficient to kill the organisms in less than one minute at 54 inches. It was further stated that this intensity would cause only a transitory erythema on a blonde subject after 80 minutes' exposure. In an experimental animal

study, adhesions in exposed viscera were said not to be increased over those of the controls. Hart has reiterated the safety of these doses in his most recent publication.[24]

The patient's course of hospitalization in Hart's reports was extremely satisfactory and showed a material reduction in postoperative temperature, and a tremendous reduction in the incidence of wound infection. Most of his cases were thoracoplasties but later other operations were reported[24] to have been performed without hazard.

On the other hand, in attempting to estimate the efficiency of radiation from a different type of generator to sterilize the air in infants' wards, Major and Wilder[33] found no appreciable difference in bacterial colony counts between a ward radiated with ultraviolet and a control ward. No mention was made of the quality or intensity of radiation.

The lay press as well as most of the medical publications[19] have described the use of ultraviolet radiation as being very efficient and any hazards connected with its use have been either neglected or minimized. It is the purpose of this paper to report our observations during four years of study and to caution surgeons who contemplate its use to determine that the radiation has the most effective bactericidal quality, that the intensity of the radiation is sufficient to materially reduce the bacterial content of the air and, not so great, over a given period of time, to do tissue damage.

Physical Considerations.—Without entering too deeply into a discussion of physics, it may be well for us to consider briefly the fundamental nature of ultraviolet radiation.[31] It will be at once apparent that the term ultraviolet "light" is a misnomer as light is only that part of radiant energy which renders objects visible. The relationship of ultraviolet radiation to visible and infra-red rays may be best appreciated by the diagram,[48] shown in Figure 1, the numerals of which are approximate values.

Ultraviolet	Visible	Infra-Red
136 Å to 3,900 Å	3,901 Å to 7,700 Å	7,701 Å to 4,000,000 Å

(An Ångström unit is 1/10,000,000 millimeter)

FIG. 1.—Showing the relationship of ultraviolet radiation to visible and infra-red rays.

To determine the "quality" or wavelength of radiation from any given source, it is necessary to examine it with a spectrograph. This consists basically of a quartz prism and an appropriately ruled scale. A photographic plate is exposed and gives the lines of emanation from the generator.

Radiant energy generators[50] are of three main types. Temperature radiators such as (1) the sun and filament lamps, which give a continuous spectrum; (2) arc lamps which radiate a mixed spectrum; and (3) vapor discharge lamps which radiate a discontinuous line spectrum (Fig. 2). Because there is more heat than ultraviolet radiation associated with the first two types of generators, it is not logical to consider them as a source for the rays with which we are now chiefly concerned. The third type, namely, vapor, and particularly mercury vapor discharge lamps, are the only ones giving a

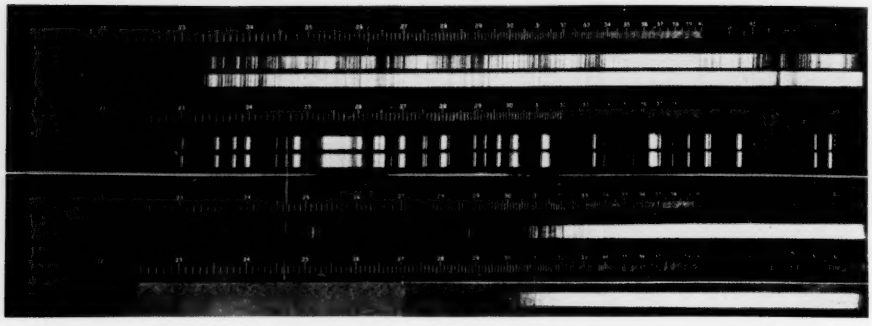


FIG. 2.—Spectrograph showing type of radiation from different types of generators (Laurens[31]). The first pair of spectrograms are of the iron arc (6 A, 35 V), exposures of 20 and 60 seconds, respectively. The second pair are of the mercury arc in quartz (5 A, 70 V), exposures of two and five seconds, respectively. The next, single, spectrogram is of the flaming carbon arc (28 A, 60 V), exposure of five seconds. The bottom spectrogram is of the sun taken on May 24, 1928, at 11 A.M., exposure of 15 seconds.

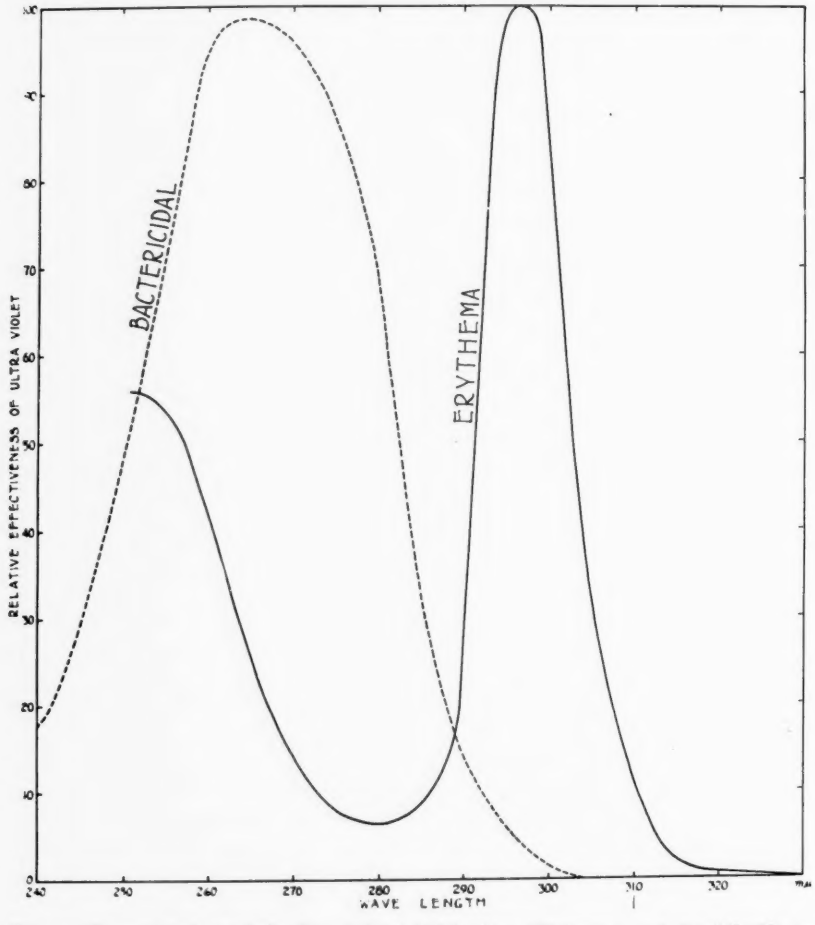


FIG. 3.—Curve showing relationship of bactericidal effect (Ehrismann and Noethling[20]) to the erythema effect (Coblentz *et al.*[15]).

large part of their radiation in the ultraviolet spectrum. However, as will be seen subsequently, not all mercury vapor discharge lamps give off the same type of radiation in this spectrum. The "quality" or length of waves emanating from such a source depends on the nature of the gas or gases and the filtration of the container in which the discharge takes place.

The physiologic effect of any wavelength of radiation is extremely critical. This is best brought out by considering the different colors in the visible part of the spectrum. From one end of the colored spectrum to the other, the violet rays differ from the red by about 35/100,000 of a millimeter. The rays yielding blue light differ in wavelength from the rays yielding green light by only 5/100,000 of a millimeter.[27] So that, when we consider radiations in the zone of shorter wavelengths, it might be expected that rays varying only slightly in length might produce quite varied physiologic results.

That there have been differences in the effectiveness of different wavelengths of the ultraviolet spectrum was appreciated at a relatively early date. Barnard and Morgan,[2] in 1903, stated that the most effective bactericidal range lay between 3,287 Å and 2,265 Å. Henri[26] also found that the action was greater as the wavelength decreased but that the short rays were less able to penetrate protoplasm. Newcomer[39] narrowed the zone of optimum bactericidal action to the region between 3,000 Å and 2,150 Å. In 1918, Bovie[7] demonstrated that paramecia were best killed at 2,800 Å. Further bactericidal work on various organisms by many observers was summarized in Coblentz'[13] work, in 1935, in which the most effective range was found to be in the shorter wavelengths and rapidly diminished at 3,650 Å. The curve of Ehrismann and Noethling[20] has its peak at 2,537 Å and diminishes to nearly zero at 3,000 Å. Coblentz[15] also studied the erythema production of various wavelengths on the untanned human skin and his curve is shown on the accompanying chart comparing it with the bactericidal effect of Ehrismann and Noethling (Fig. 3).

Many theories have been advanced regarding the photochemical effect of ultraviolet on bacteria. It was at first thought that certain wavelengths were specific for different bacteria. This assumption was not confirmed by Bayne-Jones and Van der Lingen.[4] Bedford[5] believed that the effect was obtained through the production of hydrogen peroxide within the organism. Burge[9] believed the action to be due to a coagulation of the protein rather than any action on intracellular enzymes and he demonstrated its effect on immature paramecia rather than on the more mature forms. Rentschler[45] confirmed this with respect to *Bacillus coli*, and by properly timing the cycle was able to materially reduce the amount of radiation necessary. He suggested that the effect is probably dependent on the square area exposed, as adult bacteria about to divide are almost twice as large as the young forms.

The effect of ultraviolet radiation on multicellular organisms has been appreciated for many years. Bernhard,[6] in 1902, reported the use of sunlight on wounds and was very enthusiastic in a report of its healing property in the treatment of a long-standing suppurative wound. Later, he used artificial ultraviolet for this purpose. Rollier[47] used sunlight alone very successfully in

treating patients with traumatic injuries as well as tuberculous patients. Rasero,[43] in 1922, advocated the use of an artificial quartz burner with progressive intensity in treating wounds and ulcers. Torraca,[54] from 1921 to 1924, experimenting with guinea-pigs, found that wounds exposed to sunlight healed better than others.

Before any consistent results can be obtained with a physical agent, one must know how much of this agent is being used. Inasmuch as ultraviolet radiation extends over a spectral band, it is necessary to have a method of determining how much radiation is being given off in each of the dominant bands.

A history of the various methods of measurement has been compiled by Laurens.[31] At the present time there are two main methods: (1) Those based on biologic or photochemical reactions which measure a gross intensity; and (2) those which employ accurate physical methods such as described by Coblentz.[14] He used a complicated apparatus consisting of a photo-electric cell, a balanced amplifier, and a micro-ammeter which will measure minute intensities in the various spectral bands of the sun's radiation.

A simpler form of radiometer has been developed by Rentschler[46] and accepted by the American Medical Association.[61] This has been designed to measure intensities of ultraviolet radiations from artificial sources. By altering the type of glass filter from which the bulb is made and having a metal which is sensitive to a particular wavelength range, the radiometer is given a selective range and will measure the quantity of radiation in that range. Three cells are available: the thorium, measuring the range from 3,200 to 3,700 Å; the titanium, measuring the range from 2,700 to 3,200 Å; and the tungsten, below 2,700 Å (Fig. 5). The intensity is read directly in "clicks per minute" which is an empiric value for each instrument.*

Physicists[12, 29] and manufacturers of ultraviolet generators[1, 44] were consulted and proved to be of great help in obtaining experimental equipment.

Our preliminary experiments were performed with a mercury vapor quartz tube, such as is in general use by physiotherapists. This was discarded because of its lack of mechanical adaptability. The next type of tube was more adaptable and had similar output characteristics but was of greater intensity. However, it was found to cover too wide a range of the ultraviolet spectrum including the ozone producing range. The third type attempted to correct the faults of the second by putting an outer jacket over the quartz tube, the space between containing dilute acetic acid. This jacket and fluid filtered out the shorter ozone producing rays and a large proportion of the higher wavelengths.

At this stage of our early experimental studies, a fourth ultraviolet generator was made available which was developed by James,[29] in 1930, and applied by Rentschler.[44] It has been described by Sharp[51] as a low pressure mercury vapor discharge through a glass tube permitting a "high transmission" in a narrow zone and is said to give an essentially monochromatic output

* Proper calibration for an instrument is available at the Bureau of Standards, Washington, D. C.

in the wavelength 2,537 Å, having 88 per cent in this field, the remainder lying above 2,000 A. A spectrograph of this is shown in Figure 4 and may be compared to those shown in Figure 2. The experimental generators were compared qualitatively and quantitatively by means of three different radiometers and the results show that the maximum intensity of radiation was given

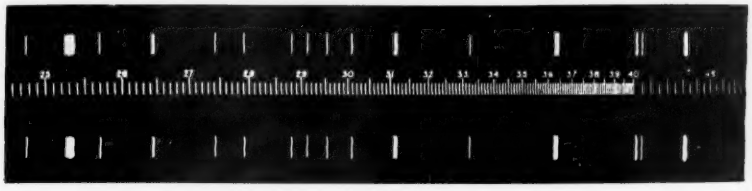


FIG. 4.—Spectrograph, with the monochromatic generator (Sharp[51]), of the lamp output at 27 Ma. of current.

off in the zone 2,000 to 2,700 Å from all three generators. The monochromatic generator and the jacketed quartz tube practically limit their rays to this zone, but the quartz burner, without the jacket, permits a considerable portion of rays in the zone 3,200 to 3,700 Å to come through and also emits the shorter ozone producing rays. This may be seen in Figure 5.

	Tungsten Tube	*Titanium Tube*	*Thorium Tube*
Range	2,000–2,700 Å	2,700–3,200 Å	3,200–3,700 Å
Distance	100 cm.	50 cm.	25 cm.
Monochromatic generator	8.8 c./m.*	0.5 c./m.	0 c./m.
Quartz burner with jacket	10.5 c./m.	1.0 c./m.	0 c./m.
Quartz burner without jacket	13.0 c./m.	1.0 c./m.	9 c./m.

* c./m. = clicks per minute.

FIG. 5.—Showing the relative time of penetration, using different tubes, between the monochromatic generator and the quartz burner both with and without a jacket.

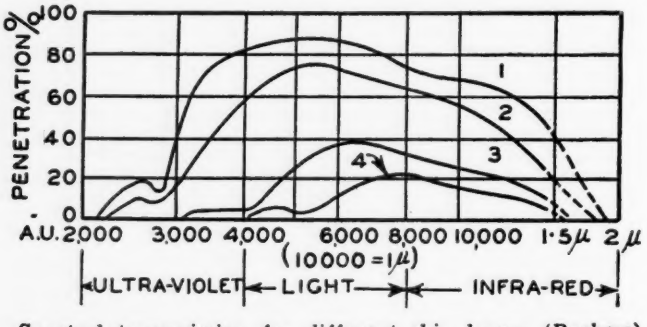
It is apparent that the jacket reduced the erythemal rays emitted by the quartz tube, although it still passed twice as much as the same intensity of the monochromatic generator. Also, the jacketed quartz tubes are much smaller than the monochromatic generators and make up for their size by an increased intensity.

Determination of Tissue Injury.—Without considering the general biologic effect on metabolism, circulation, and blood, the local effect is of considerable interest. Photochemical changes in tissue are dependent upon the absorption of the rays by those tissues. The various waves in the ultraviolet spectrum penetrate below the skin for variable depths (Fig. 6).

The two measurable chemical changes following the radiation of skin are the production of tyrosine, which forms the pigment in the skin, and the change of histadine to histamine,[28] which may be developed in sufficient quantity to produce local or general effects. When we expose visceral tissue to this radiation, the problem is somewhat different. While there is no tyrosine reaction, which probably occurs only in the skin, the histadine-histamine changes do occur and may be sufficient to cause a more profound local or

general effect. Moreover, in the skin, certain rays are filtered out, while in the visceral tissues this filtration does not occur to the same extent. It is, therefore, more important to expose visceral tissue to only those rays which are relatively harmless and for periods of time which can be tolerated.

It was thought that we might standardize the dosage of radiation by determining the quantity which produced adhesions in a loop of guinea-pig intestine. The animals were operated upon under nembutal anesthesia and aseptic precautions were observed. The abdomen was shaved and prepared with iodine, which was removed with alcohol. After proper draping, an incision was made and a loop of small intestine, approximately 8 cm. in length, was exposed to the radiations, during which time it was kept moist with saline solution. After exposure, the incisions were closed with three silk sutures through the whole wall and a dressing of collodion applied.



Spectral transmission for different skin layers (Bachem).

1. Corneum	.. ..	*0.03mm. thick*
2. Epidermis	.. ..	*0.05 „ „*
3. Epidermis and papillary	..	*0.50 „ „*
4. Epidermis and corium	..	*2.0 „ „*

The thicknesses stated correspond approximately to nature.

FIG. 6.—Penetration of skin (Seitz[50]).

The animals which survived were sacrificed after one week and the viscera examined.

As has been indicated before, our first studies were made with a rather intense quartz burner giving a high output over a wide range of the ultraviolet spectrum, as is indicated in Figure 2. Figure 7 shows a loop of guinea-pig intestine, completely gangrenous, exposed for 15 minutes at 18 inches to this generator. The jacketed tube was then used in a similar manner. This caused slight adhesions in a 15-minute exposure at 36 inches, as well as at 18 inches (Fig. 8), and is still considered a harmful effect. Further studies on adhesion production were made with the jacketed quartz tube and it was found that they were consistently produced in 15 minutes at 18, 36 and 45 inches.

Similar studies were then made with the monochromatic generator. The criterion of adhesion formation was the agglutination of loops of the exposed intestine (Fig. 9). Detailed microscopic studies were made of the effect of this radiation upon guinea-pig intestine. Figure 10 shows a cross-section of

FIG. 7.—Showing gangrene of loop of guinea-pig intestine radiated with high intensity quartz burner for 15 minutes at 18 inches.

36 inches, 15 min.

18 inches, 15 min.

FIG. 8.—Lower controls showing no adhesions. Upper specimens are exposed intestines showing adhesions produced by quartz burner with jacket.

normal guinea-pig intestine. The serosa is smooth and thin, and the relative size of the vessels may be seen in one area. The effect in a guinea-pig sacrificed two hours after radiation at an intensity of 33 clicks per minute for 15 minutes, is seen in Figure 11. This section shows a red and white cell extravasation just beneath the delicate serosal layer with slightly enlarged vessels and edema developing in the walls. Employing the same dosage, an animal, sacrificed 24 hours after radiation (Fig. 12), shows the edema and blebs to be more evident as well as the tremendous dilatation of the vessels surrounded by an edematous mesentery. A more advanced reaction is to be seen after three days (Fig. 13), in which there is also evidence of degeneration of the glandular elements. At the end of a week, a section (Fig. 14) taken through an area of adhesion shows extensive glandular destruction. A higher magnification of Figure 14 shows that the fibrinous adhesions are beginning to organize although evidences of inflammatory reaction still persist (Fig. 15).

FIG. 9.—Showing adhesions produced by the monochromatic generator—54 inches, 33 clicks per minute for 15 minutes.

Because of these reactions, it was felt that it was important to determine just how much radiation the viscera could tolerate of different intensities for varying periods of exposure. The results of this study are recorded in Figure 16. The numerator of the fractions indicates the incidence of adhesion formation and the denominator the total number of animals exposed at the particular intensity and period of time indicated. From this information a curve of safety was drawn below which it was felt that exposure would not produce adhesions. It will be noted that after one hour, five out of 11 control animals developed adhesions although the intestines were kept moist with saline solution during the entire time. Therefore, this was taken as the longest time to expose viscera safely to air without radiation.

Determination of Bactericidal Action.—Having determined the safe zone of exposure in terms of intensity and time, it was necessary to plot the previously determined bactericidal effect at these same intensities and times. This was done using *Streptococcus haemolyticus, Bacillus coli, Staphylococcus aureus, Streptococcus viridans,* and *Bacillus subtilis.* The method was as follows: A blood agar plate was sprayed with a 24-hour culture of organisms diluted 1:100, the Petri dish was covered with cardboard except for a small square opening in the center, and the exposures were made for the indicated intensity and time. One determination, on *Staphylococcus aureus,* is shown in Figure 17. The end-point for this particular determination is six minutes

FIG. 10.—Cross-section of normal guinea-pig intestine.

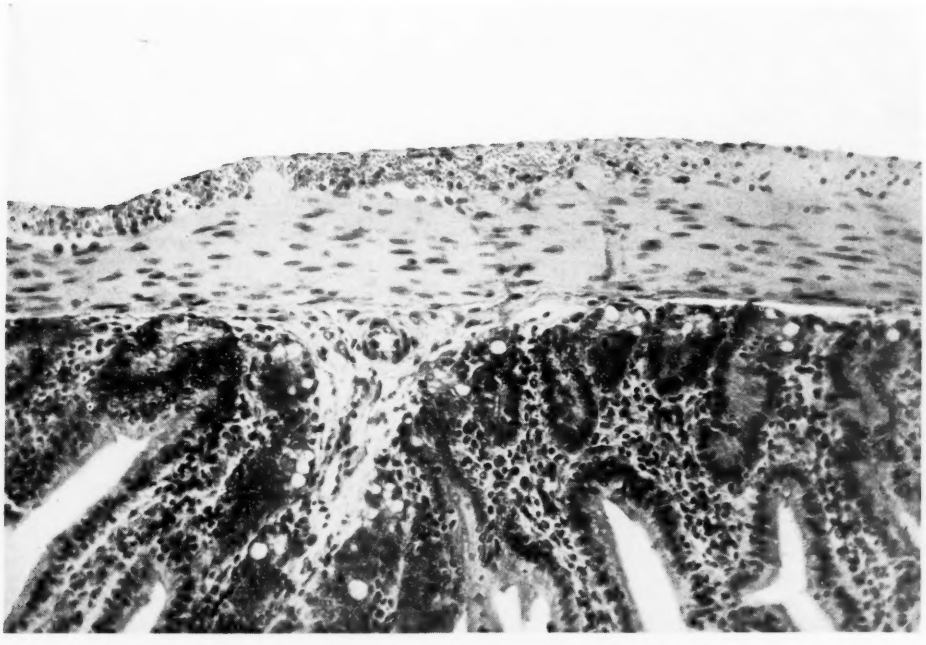


FIG. 11.—Photomicrograph, two hours after radiation, showing leukocytic and red cell extravasation beneath serosa. (High power)

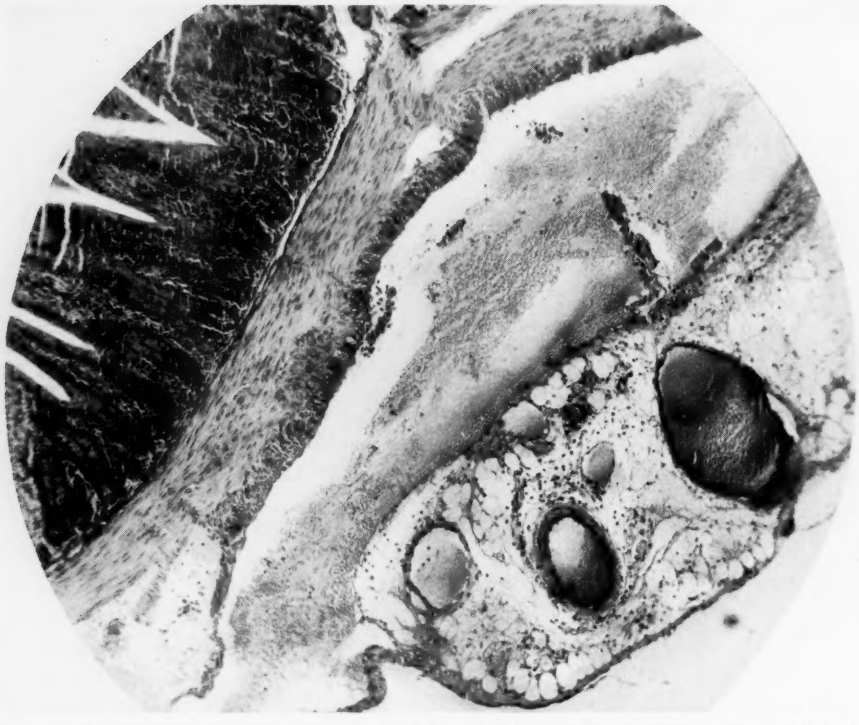


FIG. 12.—Photomicrograph, one day after radiation, showing the development of subserosal blebs and greater hyperemia.

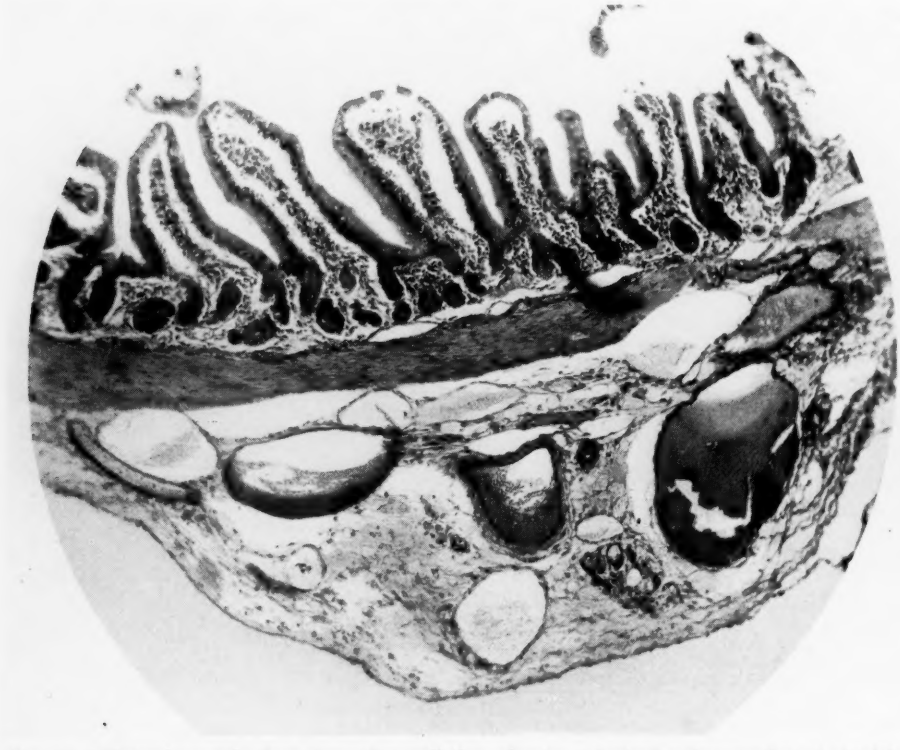


FIG. 13.—Photomicrograph, three days after radiation, showing a beginning degeneration of glandular elements.

FIG. 14.—One week after radiation. Section taken through adhesion. Note extensive glandular destruction. (Low power)

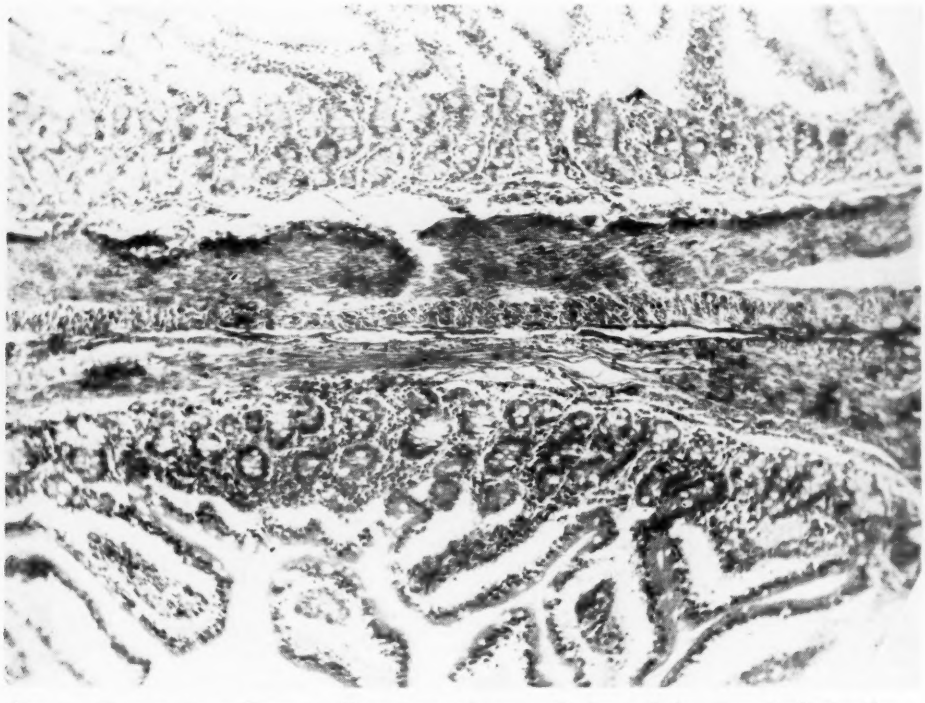


FIG. 15.—Same section as Figure 14: Photomicrograph, one week after radiation, through adhesion showing firm agglutination with fibrin and beginning organization at the margins. (High power)

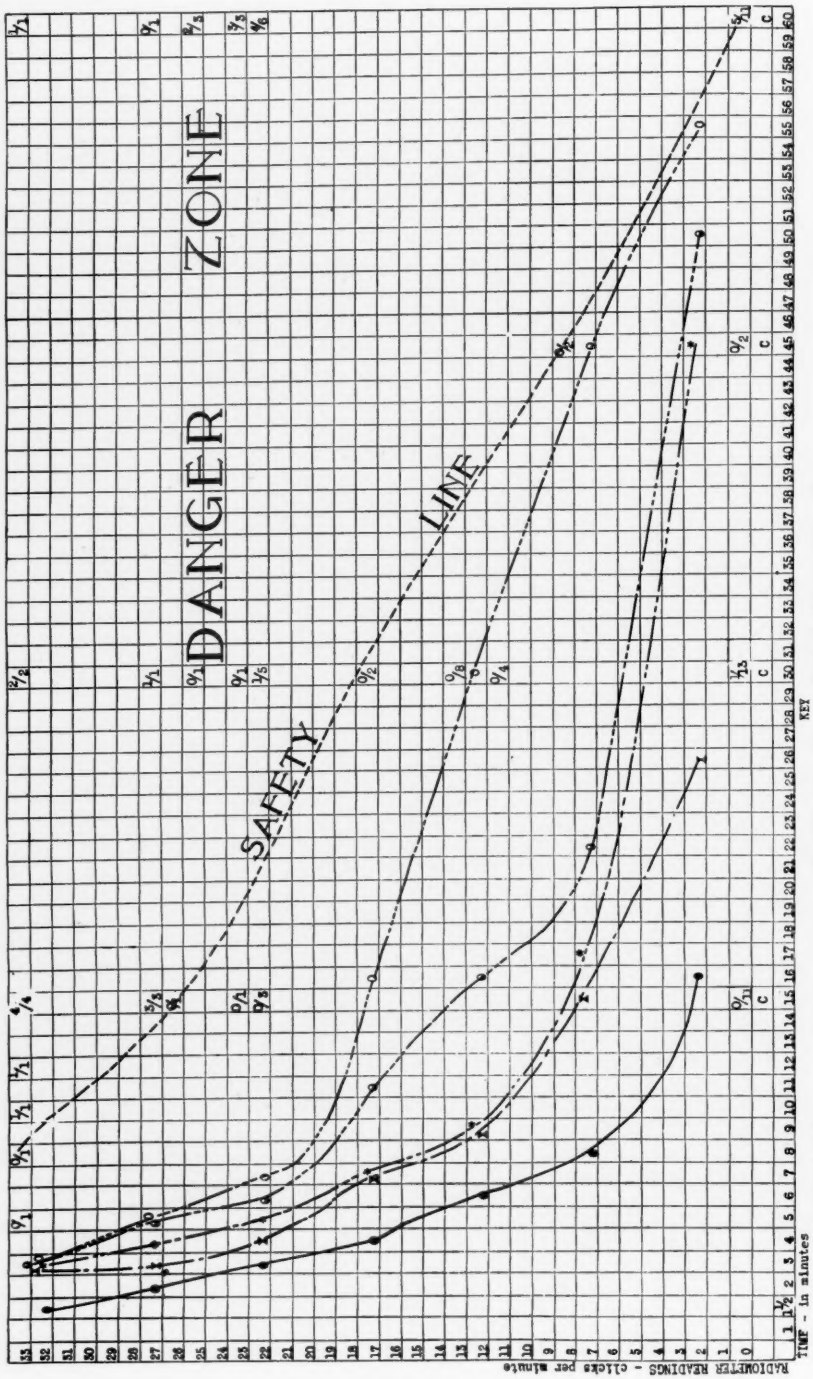

DANGER ZONE
SAFETY LINE
RADIOMETER READINGS - clicks per minute
TIME - in minutes
KEY
Staphlococcus - *
Bacillus Coli - X
Bacillus Subtillis - 0
Hemolytic Streptococcus - ●
Streptococcus Viridans - ●
C = Control animals
0/0 = Number of adhesions / Number of animals exposed.
Total number animals exposed - 56.
Total number control animals - 57.

FIG. 16.—Comparative graph showing intensity required to sterilize organisms on seeded plates and that required to produce adhesions in guinea-pig viscera. (1 click = 1.71 microwatts per square centimeter at 1 meter)

as the square is seen to have a sharp outline. The average of a number of similar experiments indicated complete bactericidal action for *Staphylococcus aureus* to be five minutes at 22 clicks per minute. It will be seen that the

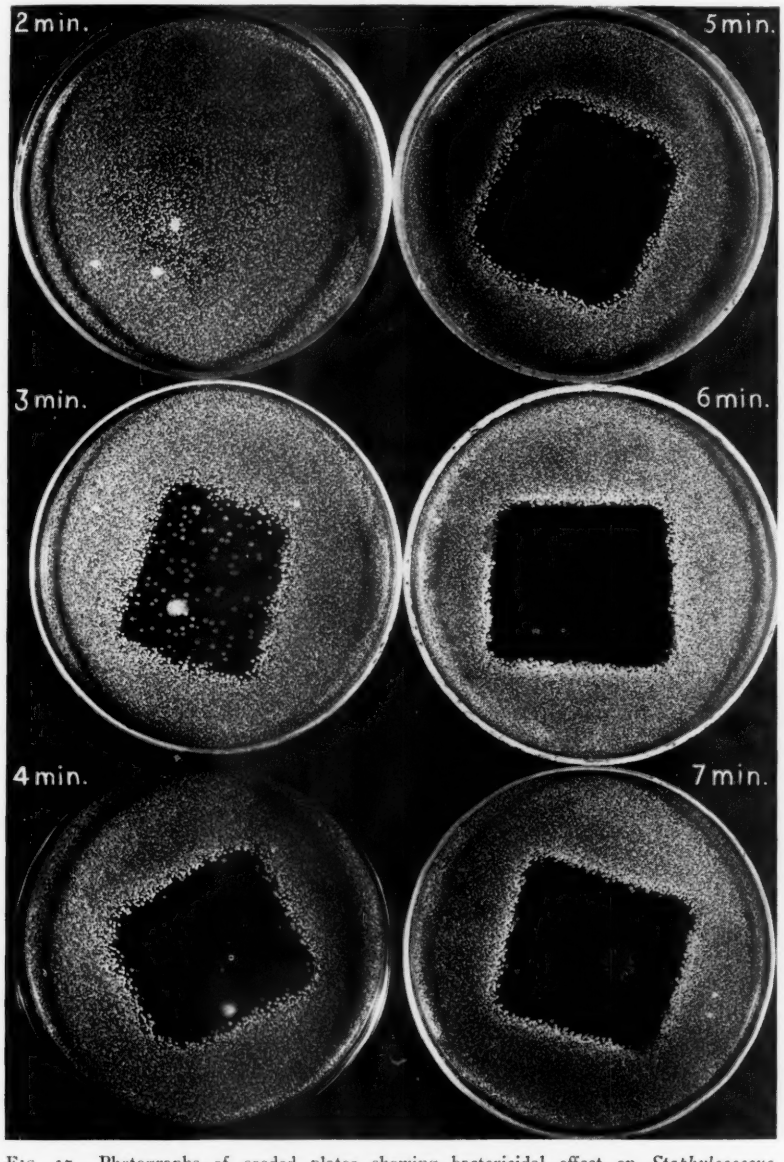


FIG. 17.—Photographs of seeded plates showing bactericidal effect on *Staphylococcus aureus*. Intensity 22 clicks per minute—end-point six minutes.

lethal points for all organisms fall below the safety line so that there is an adequate margin of safety. It is evident, therefore, that one may still kill organisms on seeded plates with a lesser intensity than that which will injure guinea-pig viscera in the same period of time.

Our problem was to determine the effect of this relationship to the bac-

tericidal effect on organisms suspended in the air. Here we found confusing factors, such as variations in the air currents, size of droplets of organisms, and hazards to exposure from the organisms themselves. Many experiments were undertaken in an attempt to obtain consistent results, but it was not until a chamber was constructed, as is shown in Figure 18, that any significant data was obtained.

This apparatus consisted of a large upper chamber four feet square with a corresponding space below divided into two parts and separated from one another longitudinally by a partition. The side of one of the lower compart-

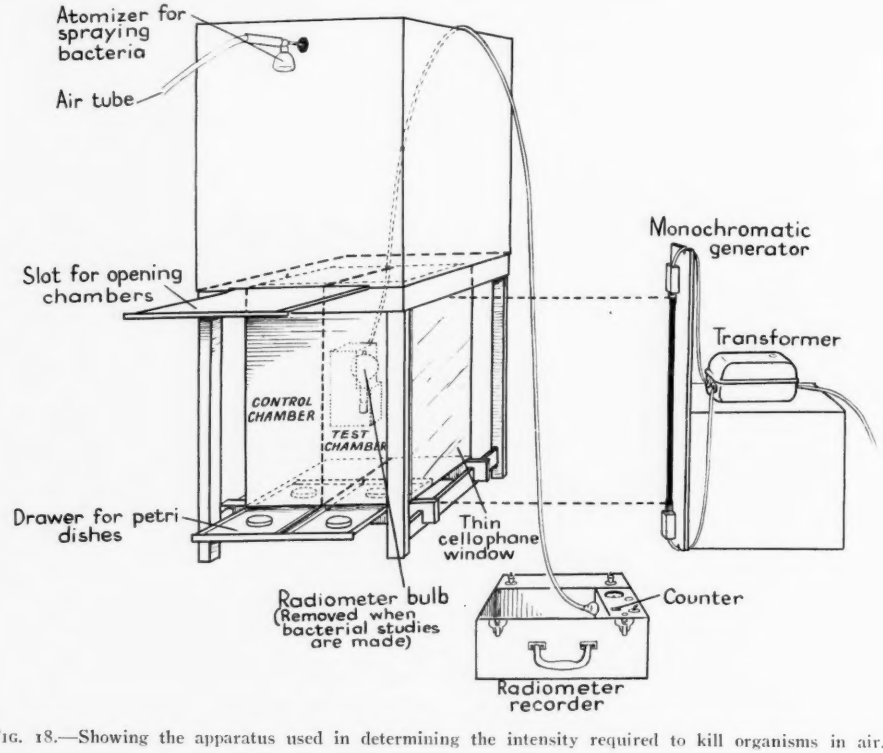


FIG. 18.—Showing the apparatus used in determining the intensity required to kill organisms in air.

ments was made of a thin cellophane window in order to permit the passage of ultraviolet radiation from a monochromatic generator nearby. A drawer on the floor of the two lower compartments made it possible to expose Petri dishes and collect falling bacteria. Preliminary tests showed that an approximately equal number of bacteria fell and grew on the Petri dishes exposed in the drawers of the two lower compartments. The upper chamber was sprayed with 10 cc. of a 24-hour culture of bacteria diluted 1:100, which represented approximately ten to 50 million organisms per cubic centimeter. It was found that one minute settling time of the bacterial spray in the upper chamber was necessary to evaporate the fluid part of the culture and prevent droplets from forming on the exposed plates in the lower drawers. The tops of the Petri dishes were opened after the radiation was discontinued,

insuring the fact that the organisms were not destroyed after they had settled on the culture media of the dish. The plates exposed in the control chamber and those exposed in the radiated chamber were then compared.

The intensity of radiation was regulated by altering the distance of the monochromatic generator. It was found that there was not as definite an end-point of lethal action in these tests as there was in the exposure of the seeded plate. Some effect was present at as low an intensity as four clicks per minute. These tests were performed at different times so that the colony counts on the control plates vary considerably, though we may assume that the number of bacteria falling in the control and in the radiated chambers were the same in any given test. The relationships are shown in Figure 19.

	Test	*Control*
4 c./m.	51 colonies in 1 minute	356 colonies in 1 minute
6 c./m.	26 colonies in 1 minute	118 colonies in 1 minute
10 c./m.	6 colonies in 1 minute	220 colonies in 1 minute
13 c./m.	3 colonies in 1 minute	535 colonies in 1 minute
16 c./m.	2 colonies in 1 minute	327 colonies in 1 minute

FIG. 19.—Shows the effect of ultraviolet radiation on bacteria suspended in air.

Employing this method of determining bactericidal power in air, variations were made in the time of exposure, time of settling, and intensity of radiation. We found that an intensity of 13 clicks per minute is required to kill bacteria falling a distance of three feet in one minute through the air, while it takes approximately nine minutes to kill the same type of organism on the seeded plate. It may be said, therefore, that, at this intensity, the radiations are nine times as effective in air as on the plate. If the intensity is raised to 16 clicks per minute the effect in the air is only six times as efficient as on the seeded plate.

Sharp[51] also studied the bactericidal power in air of this monochromatic generator, by means of a rather complicated apparatus which forced artificially contaminated air, after radiation, through liquid culture media. This indicated absolute sterility because only one or two surviving organisms would cloud the media if they were not completely destroyed. He expressed the lethal intensity as 26,200 ergs per square centimeter, while Gates[21] computed it in a similar manner as 30,000 ergs per square centimeter necessary to produce sterilization on the seeded plate. In a subsequent publication, Sharp[52] stated that in his opinion the radiant energy required to kill various organisms on the seeded plate with the monochromatic generator should be used as an indication of the killing power in air. Our experiments show that almost complete sterility is obtained much more easily in the air than on the seeded plate.

In studying Hart's[23, 24] publications it was felt that the intensity of the radiation that he used is greater than is necessary to reduce the organisms in the air and may be in the danger zone with regard to tissue injury. As his generators were of the same type which we have used, we have calculated that the intensity of Hart's radiation at a distance of five feet was approxi-

mately 33 clicks per minute. Our statistics indicate that this is almost three times as great as animal tissues may be safely exposed to for forty minutes. The actual time of exposure used by Hart was less as pads were probably used for protection.

Another apparent inconsistency was the fact that Hart found a blonde subject suffered only mild erythema after 80 minutes' exposure at this assumed intensity of 33 clicks per minute. We found that at this intensity slight erythema was produced on the inner aspect of the human arm of a blonde subject in six minutes, becoming marked at nine minutes and intense at 15 minutes. Other determinations with less intensity for longer periods indicated that one hour's exposure at 13 clicks per minute is the upper limit of safety to avoid erythema.

Practical Applications.—Air contamination in an operating room may be determined in a number of ways. Wells[60] has devised a suction apparatus with which he may take samples of a given quantity of air in an operating room. The organisms contained therein are deposited directly on an agar surface where they may be cultured, but there must be considerable quantities in the air before significant results can be obtained.

A simple method, and one which is more indicative of the contamination of a sterile field as it actually occurs, is to expose a blood agar plate on or near the sterile field of operation. Incubation then will give an indication of what might be expected to fall on the operative wound. Some of these organisms may receive further radiation after they have fallen but no known experimentation has been devised to determine the quantity of organisms which will survive this combined radiation. Flushing of the wounds with sterile saline and subsequent culturing will give an indication of contamination but will not tell how many organisms will have produced it.

Colony counts made in our operating rooms with exposed Petri dishes showed a predominance of *Staphylococcus albus, Staphylococcus aureus,* both hemolytic and nonhemolytic *Streptotoccus, Streptococcus viridans,* and *Staphylococcus citreus.*

As has been indicated before, the actual number of colonies varied considerably and depended upon the length of time of exposure, the position of the culture plate, and the number of people in the room, and their activity. In one instance a count of 280 colonies was obtained on one Petri dish in front of a group of students in 30 minutes. In another instance, in a different operating room, there were 66 colonies collected in 165 minutes. An average was made of ten determinations in one operating room and it was found that approximately 0.25 colony fell per minute per plate. In another operating room the average of 74 plates was 1.9 colonies per minute per plate.

Since the whole object of bactericidal effort in surgery is to reduce wound infection, we have, at this hospital, in the last 14 years, employed various improvements in technic, with the result of a lowering of wound infection in clean operative wounds from 4 per cent serious and 10 per cent trivial in 1925, to 0.5 per cent serious and 1.6 per cent trivial in 1938. Although this is rela-

tively low we believe every effort should be made to further reduce it. The only effort to combat air contamination during this period was to cover the instrument and dressing tables with canopies while they were not actually in use.

Our first endeavors to find an answer to the problem began in August, 1935, but it was not until January, 1937, that an installation was made in one of our operating rooms. This consisted of four one-foot quartz tubes jacketed with high transmission glass and containing dilute acetic acid between the glass tubes, previously described. This gave the maximum spectrum in the bactericidal range as indicated in Figure 5. Its intensity was very slight at the operative field, registering a total of only five clicks per minute with the tungsten bulb. This was reduced to zero when the operating team shielded the radiometer, but the reduction of the bacteria in the air was definite. Sixty-two plates were exposed in four cardinal positions, giving a total of 1,692 colonies collected in 955 minutes. This gives an average of 0.029 colony per minute per plate. Encouraged by the decrease in the number of viable organisms in the air and knowing that little if any tissue damage could come from radiation of such low intensity, various types of operations were performed under it.

Of over 100 major operations performed under these generators, 52 could be classified as clean cases and only one of these developed a minor skin infection. This, of course, is a very small number from which to draw any conclusions, but a careful study of the postoperative temperature reactions revealed no appreciable lowering of the average.

The operating room staff were provided with clear glass auto-driving goggles to protect their eyes from conjunctivitis. Ordinary spectacles did not protect them from the lateral rays. A simple starched helmet seemed to be all that was necessary to cover the head but this did not protect the forehead and areas left exposed by the mask. It is now recommended that a wide brim helmet be worn with a safari-type cloth to cover the back of the neck for more adequate protection.

Development of Present Application.—We were not entirely satisfied with the previously described ultraviolet generator arrangement because we felt that there should be a sufficient concentration of radiation at the area immediately above the operative wound. We also felt that a wider distribution of a lower intensity of the proper radiations would be more efficient in reducing general air contamination. Although it was impossible to put a culture dish just where it would be most significant, dishes hung in baskets from the margin of the lighting unit usually gave the highest counts.

Effort was spent for several years to alter an illuminating unit to include an ultraviolet installation with a fan so placed that it would draw the air upward into the zone of the radiation. At the convention of the American College of Surgeons, in October, 1937, an operating room light was displayed which had no cover and made use of the 250 watt bulb with its heat-absorbing filter to promote an upward current of the air. The possibility of utilizing this

principle was at once appreciated, and after some time a unit was developed with an ultraviolet generator built in the lower margin. It was hoped that the gentle upward current of air would draw any bacteria in the air immediately above the operative wound slowly through the unit so that they might be destroyed while approximating the more intense radiation. First, it was necessary to determine whether or not the rising column of air was strong enough to make the bacteria rise. Culture plates were suspended from the unit with the top closed. Experimental studies were undertaken by spraying bacteria into the air and counting those which fell and grew on Petri dishes exposed at various levels between the unit and the operating table. The illuminating light was turned on, the top opened allowing the air to pass as it normally would, and another series of similar tests made. It was evident that there were many more organisms on the 52-inch plate when the top was closed and on the 12-inch plate when the top was opened, indicating that they were then drawn upward through the cone of the illuminating unit.

Distance	*No Illumination* (*Top Covered*)	*Illuminating Unit Operating* (*Top Open*)
12 inches	142 colonies	995 colonies
24 inches	143 colonies	391 colonies
36 inches	354 colonies	272 colonies
48 inches	511 colonies	312 colonies
52 inches	191 colonies	246 colonies

FIG. 20.—Shows that air currents developed by the functioning illuminating unit draw bacteria upward.

It is apparent that the maximum intensity of the radiation should be above the operative site opposite the exhalations of the operating team, rather than directly on the wound itself. This was accomplished by the design of the reflectors in the illuminating light. At the operative site the intensity was considered to be optimum at 13 clicks per minute which has been calculated to kill 99.50 per cent of the organisms in air suspended for one minute. This is about the time an organism will take to drop a distance of three feet in still air. With this illuminating unit and its ultraviolet generator, if the organisms were not drawn through it and killed, the air currents would suspend them longer than one minute and practically insure their destruction. At this same intensity, our experimental animal studies have shown that guinea-pig viscera, which is probably more sensitive than human viscera, will not show changes after 40 minutes' exposure. This would probably exceed the actual time of continuous exposure of any one portion of a patient's viscera during any type of operation.

As has been indicated by Nisbet,[40] and confirmed here, the greatest contamination of the air occurs when the patient is being prepared by the many people who are hurrying about performing their duties, but at the same time stirring up a considerable number of organisms. It was felt that a greater intensity of radiation should be used at this time and gradually reduced as the activity in the room decreased. This would reduce the intensity of the radiation on the exposed viscera and would be adequate to keep the air relatively

sterile as the contamination decreased. It has been possible to install a regulating device on the ultraviolet generator which will regulate the intensity of radiation as required by an automatic time clock, or it may be manually controlled for unexpected prolongation of the operation.

Auxiliary units are placed on the walls in such a manner that sufficient intensity is developed throughout the room to keep the air relatively sterile. Each unit consists of a 30-inch generator with a control to regulate its intensity. It is therefore possible, with the use of a radiometer, to accurately determine the radiation in any part of the room and to raise it or lower it depending upon requirements.

Such an installation was set up in the laboratory and further bactericidal and adhesion determinations made. For example, eight animals were exposed

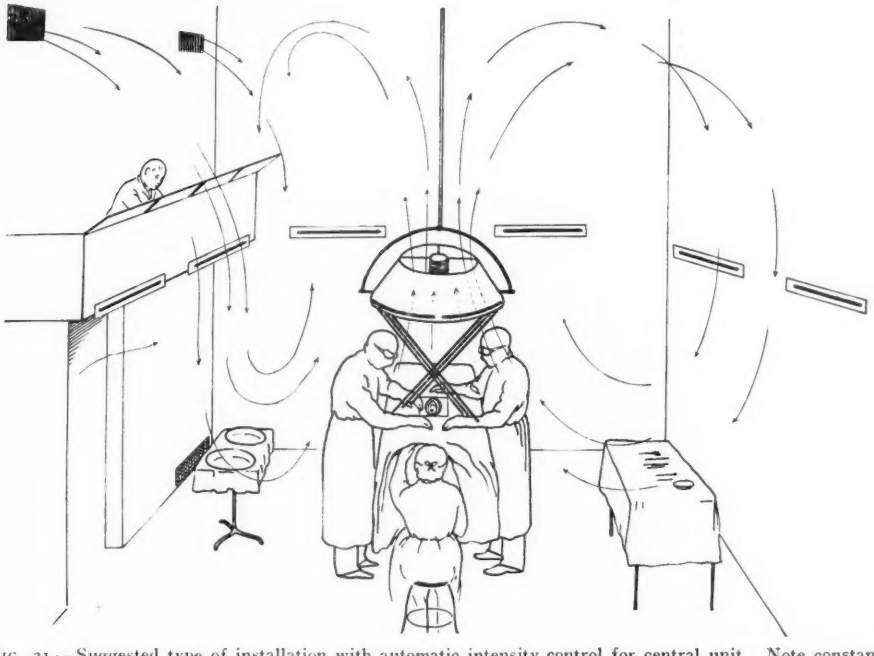


FIG. 21.—Suggested type of installation with automatic intensity control for central unit. Note constant intensity over basins and instrument table.

at 13 clicks per minute for 30 minutes, and at autopsy, one week later, showed no evidence of adhesion. Bactericidal determinations at different stations in the room were made using seeded agar plates, similar to the previously described seeded plates. These findings have been recorded in Figure 16. It was felt, therefore, that this type of installation (Fig. 21) was safe and effective in controlling air-borne organisms and would not injure exposed viscera.

Effect on Wound Healing.—The remaining question for consideration is the effect of ultraviolet radiation on wound healing. It is self-evident that a wound which received no bacterial contamination may logically be expected to heal more quickly and with less reaction than a contaminated wound even

though it did not suppurate. Any lessening of contamination will have a proportionately favorable effect. However, some observers believed that the radiation has a beneficial effect on the wound itself. As has been mentioned above, Bernhard[6] employed sunlight, in 1902, and later, an artificial source of ultraviolet radiation. Many other surgeons have used it empirically. Considerable interest was stimulated by Havlicek,[25] who employed a particular wavelength through a Woods' filter (366 Å) in treating cases of peritonitis. He stated that the action is not bactericidal but due to vasodilatation and subsequent prevention of thrombosis. This method and that of infra-red were studied by Bastien,[3] who felt that a combination of the two was important.

Recently, Pollaczek[41] investigated, both clinically and experimentally, the use of controlled amounts of radiation on wound healing from a lamp produced by a "Wolframel" burner. This gives a combination of infra-red, visible, and ultraviolet rays. He found that a small amount of radiation was definitely beneficial while a larger amount retarded wound healing.

Markuze[34] attributed the improvement in wound healing to a general effect more than a local effect, and found that the improvement over the controls was more demonstrable in older groups where epithelization is slower.

The direct action of various wavelengths on tissue cultures has been studied by Mayer and Schreiber.[35] They found that tissue cultures are not affected by wavelengths above 3,130 Å but are damaged considerably by radiations in the range 3,130 to 2,970 Å. Shorter radiations have less effect down to wavelengths below 2,800 Å where it remains approximately constant. This follows the erythema curve closely and may be due to histamine liberation.

In this laboratory, animal wounds, both clean and infected, were treated with the monochromatic generator. These, studied microscopically, showed an increase in vascularity, and the impression was also obtained that there was an advance in the stage of wound healing as compared with controls. No significant differences were appreciated in artificially contaminated wounds but the question remains whether or not some of the improvements in wound healing, described by Hart,[24] may be attributed to this effect as well as reduction in air contamination. However, the effect of the various wavelengths of ultraviolet radiation on healing wounds forms a study in itself and will be reported upon later.

CONCLUSIONS

(1) The unsterile air in the operating room is an important source of wound contamination.

(2) This contamination may be practically eliminated by the use of ultraviolet radiation, in the proper spectrum, with an intensity that will not injure animal tissue exposed for the time of a usual operation.

(3) An ultraviolet generator has been applied to an illuminating unit which concentrates this radiation in the most critical area, automatically controls the intensity of radiation, and, when bacterial concentration is greatest, produces the maximum effect.

(4) If the use of ultraviolet radiation for reducing air contamination in operating rooms is contemplated, surgeons are cautioned to determine that the quality of the radiation is in the most efficient part of the spectrum, and that the intensity is great enough to render the air relatively sterile and yet not so great that it will injure tissue for the period of time it will be exposed.

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THE MILLER-ABBOTT TUBE AS AN ADJUNCT TO SURGERY OF SMALL INTESTINAL OBSTRUCTIONS

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GASTRIC and duodenal suction has been used extensively during the past 20 years in the treatment of acute ileus. Kussmaul and Cahn[1] (1884) first used an elastic stomach tube for aspirating purposes and reported that this treatment would diminish the intra-abdominal pressure, reduce the size of the bowel proximal to the point of obstruction, and retard violent peristalsis. The duodenal tube was used by Westerman[2] (1910) for the distention of peritonitis, and McIver and his coworkers[3] (1926) used it as a prophylaxis against postoperative ileus, after demonstrating that the source of gas in these cases was largely swallowed air. Wangensteen[4] (1933) increased the effectiveness of the method by introducing the continuous suction-siphonage apparatus attached to the Levine gastroduodenal catheter. Wangensteen and Paine[5] (1934) reported a low mortality in a large group of cases with acute ileus that were treated with continuous duodenal suction and surgery if necessary, and for the first time pointed out the type of cases that could be successfully deflated.

Wangensteen's[6] classic work on bowel obstruction emphasized the importance of duodenal suction as an aid in the diagnosis as well as the treatment of these cases. He also recognized the obvious limitations of the method and stated that the most important objections were the inability to feed the patient by mouth, the continuous loss of electrolytes, and the failure to deflate the patient who had no peristalsis to regurgitate the fluid and gas into the duodenum. Abbott and Johnston[7] adapted the Miller-Abbott tube[8] to the management of cases with small intestinal obstructions, and reported that the limitations of duodenal suction were avoided.

Van Beuren and Smith[9] found that the mortality for acute ileus in this hospital dropped from 66 per cent during the five-year period of 1919–1924 to 29.6 per cent in 1932–1937. During the more recent period, continuous duodenal suction had been used in almost every case. In addition, the importance of replacing the fluids and electrolytes lost by vomiting and suction was generally recognized, due to the observations of many investigators. Among the more important communications are those by Hartwell and Hoguet,[10] Gamble and coworkers,[11] McIver,[12] and in this hospital, Atchley.[13] This gratifying reduction in the mortality of acute ileus has been reduced to 5.9 per cent in 68 cases successfully treated with the Miller-Abbott tube during

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the past 18 months. In fact, small intestinal intubation has proved such a valuable aid in the diagnosis and treatment of cases with small bowel obstructions that the Miller-Abbott method has been accepted in this hospital as a routine adjunct to the surgical management of all cases except those suspected of mesenteric vascular occlusion or strangulated bowel.

The Miller-Abbott Principle.—Miller[14] has recently described the development of the Miller-Abbott method of small intestinal intubation. His interest in intestinal intubation followed the report of Einhorn,[15] in 1921, of a small jointed tube used for aspirating jejunal and ileal contents. This tube, however, proved unsatisfactory in Miller's clinic, as several days were often required to pass the tip of the tube into the terminal ileum of normal individuals, and because of the small caliber of the tube. Several modifications of the Einhorn tube were equally unsatisfactory, and it was not until 1934 that Miller and Abbott[8] found a practical solution of the problem. Abbott, endeavoring to obtain kymographic records from an inflated balloon in the duodenum, found his efforts repeatedly frustrated by the rapid passage of the balloon into the jejunum. It immediately occurred to Miller and Abbott that a second larger tube for aspirating purposes could be attached alongside the smaller tube which controlled the balloon. They found that such an apparatus would reach the lower ileum within a few hours, and subsequently were able to have manufactured a double-lumened tube, one lumen for the control of the balloon and the other for aspirating gases and fluids.* This commercially prepared tube has been used exclusively in this hospital, but Abbott stresses the point that satisfactory double tubes can be prepared with the equipment available in most hospitals.

After much experimental work[16] with the Miller-Abbott tube, Abbott (Miller[14]) adopted the technic to the management of cases with intestinal obstructions. The first 16 cases treated were reported by Abbott and Johnston,[7] in 1938. Abbott,[17] in Philadelphia, and Johnston and his coworkers,[18] in Detroit, have continued the work in a large number of cases with amazing success.

Procedure.—With the balloon folded umbrella-like upon the tip of the tube and generously lubricated, the tip is passed through the nose into the nasopharynx. The patient is given a drink of water and, as he swallows, the tube is passed rapidly into the stomach. Rarely has it been necessary to pass the tube through the nose and out the mouth before attaching the balloon. A 2 per cent cocaine spray is often used to shrink the nasal mucous membrane but no effort is made to secure complete anesthesia as the patient may complain of greater pain when sensation eventually returns.

After aspirating the gastric contents, the tip of the tube is placed at the cardia of the stomach by inflating the balloon (Abbott[19]) and withdrawing it until it is stopped by the cardiac sphincter. The balloon is deflated, continuous suction by a modified Wangensteen apparatus is started, and the patient al-

* The George P. Pilling & Son Company, Philadelphia, Pa.

lowed clear fluids by mouth. It is important to allow clear fluids by mouth immediately, otherwise the tip of the tube is arrested along the greater curvature of the stomach by the thick, tenacious gastric secretions. During the next four to six hours, the patient is instructed to push in the tube slowly from the 45 cm. mark to the 75 cm. mark, preferably, but not necessarily, while lying slightly on the right side. Occasional deep breaths aid in advancing the tip of the tube into the pylorus by changing the position of the stomach if more of the tube is pushed in on the expiratory phase of respiration. The nurse is instructed to detach the suction and lavage the stomach with 50 to 100 cc. of warm water once or twice every hour to aid in decompressing the stomach.

This preliminary treatment, alone, affords so much relief that the patient will gladly cooperate if additional procedures are necessary in the fluoroscopic room. Approximately one-half the cases will pass the tube into the duodenum during this period. The position of the tip can be determined without fluoroscopic guidance by the tests described by Abbott: First, the return of the clear bile or small intestinal contents in the suction. Second, by observing the time required for water taken by mouth to appear in the suction bottle. If the tip is in the stomach, the return is instantaneous and clear, but should it have reached the duodenum, the water returns only after a delay and is usually bile-stained, never clear. Third,[18] by observing the gentle, rhythmic resistance transmitted to a smooth piston Luer syringe when the balloon is inflated with the initial 20 cc. of air if the tube is in the duodenum, in contrast to the lack of all sense of resistance when the balloon lies in the stomach.

If the tube remains in the stomach after this preliminary period, and the patient is too ill to allow fluoroscopic guidance, the procedure is repeated. This blind method of intubation has required as long as 72 hours in a patient dangerously ill with diffusing peritonitis. It is well to point out, however, that the benefits to be derived from early intubation far outweigh any temporary discomfort caused a sick patient by transportation to the fluoroscopic room, and the surgeons in this hospital now accept this procedure as a matter of course.

Our usual procedure, therefore, when the balloon remains in the stomach after the preliminary period of deflation, is to guide it to the pylorus under fluoroscopic control. An attempt is made to place the balloon at the pylorus with a wide, unkinked loop along the greater curvature of the stomach. This is accomplished by turning the patient on the right and left sides, as the occasion requires, and pushing in more tube as indicated. Manual pressure on the abdomen is seldom necessary. Not more than five to ten minutes should be spent attempting to pass the tube through the pylorus, as the position shown in Figure 1A is satisfactory.

The tube is fixed in this position with flamed adhesive tape across the upper lip, and the patient returned to his room. It is important that the tube be fixed with adhesive tape at the nose, in order to prevent it from being pushed backward instead of forward. The nurses continue their continuous suction and periodic lavage of the stomach, and the patient is allowed clear

fluids by mouth. The tip of the tube in this position (Fig. 1A) can only move forward for a distance equal to the unkinked loop in the stomach, and, as the stomach regains tone by deflation, the antral systoles invariably carry the tip into the duodenum within six to 24 hours. If fluoroscopic examination is indicated, only short, interrupted fluoroscopic exposures are necessary.

There is always a temptation to push in more of the tube after the position shown in Figure 1A has been attained and the patient returned to his bed. If this is done, however, it only causes larger loops to form in the stomach

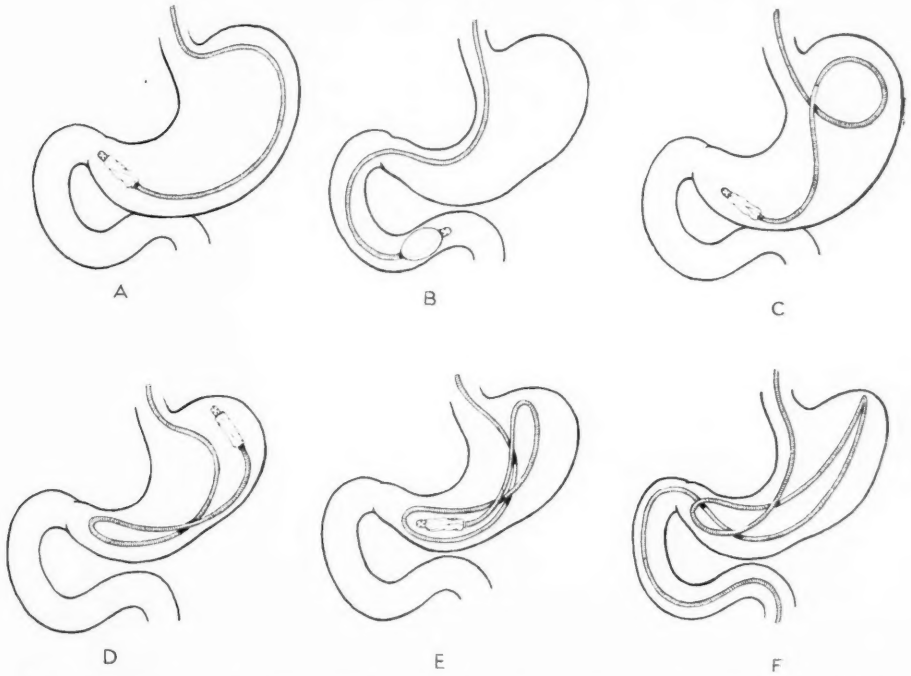

FIG. 1.—The tip of the Miller-Abbott tube at the pylorus with a wide, unkinked loop along the greater curvature of the stomach. The tube fixed in this position (A) with adhesive tape at the nose will pass the tip into the duodenum (B) after continuous suction and repeated gastric lavage has deflated the stomach and restored normal antral systoles. Additional tube in the stomach will cause the tip to fall away from the pylorus (C) and back into the fundus (D) or cause snarling or knotting (E) of the tube. The balloon is inflated with 20 to 30 cc. of air after it reaches the third portion of the duodenum (B) and thereafter the forward progress is almost automatic. Again, pushing in the tube too rapidly may cause a sharp angulation of the tube in the stomach (F) which occludes the lumen and retards the forward progress.

which tend to pull the tip away from the pylorus rather than advance it, or even cause snarling or knotting of the tube in the stomach as shown in Figures 1C, D and E. The straight unkinked loop along the greater curvature allows ample slack to reach the third portion of the duodenum when the tube arranges itself in the shorter course along the lesser curvature and into the duodenum (Fig. 1B).

If there should be trouble in passing the tube across the spine to the pylorus, in case the stomach hangs across this structure in a saddle-bag manner, turning the patient more to the right side will usually overcome this difficulty. The method described by Abbott[19] of filling the stomach with water, turning

the patient to the left side, inflating the balloon and floating the tip across the midline, has been used successfully, but usually, this is not necessary.

When the tip of the tube has reached the third portion of the duodenum and the balloon inflated with 20 to 30 cc. of air, the forward progress of the tube thereafter is almost automatic. Continuous suction is maintained and periodic lavage is continued. Often the fluid content of an obstructed loop is too thick for the continuous suction to evacuate without the aid of dilution by lavage. The patient is instructed to push in an additional six inches of the tube every one or two hours, or whenever he feels the tube tugging against his nose as it attempts to advance forward. The vigorous peristalsis of mechanical obstructions often draws the tube forward spontaneously and rapidly. On the other hand, the cases with paralytic ileus move the balloon forward very slowly. If additional tube length causes gagging when pushed into the nose, sufficient slack is present in the stomach. Additional coils in the stomach should not be allowed, as this may cause kinking (Fig. 1F) or even prolapse a loop of the tube into the duodenum, thereby interfering with suction and retarding forward progress.

After the tube has entered the small bowel, the patient is allowed a fluid diet for the first one or two days and then offered a low residue diet. All fluids aspirated are carefully charted and the oral intake of fluid is supplemented by the subcutaneous or intravenous routes. Necessary electrolytes may be replaced by giving sodium chloride capsules by mouth. Abbott[19] recommends that the amount should be aproximately 5 Gm. per liter of fluid aspirated by suction. Approximately two-thirds of the oral intake of fluid by mouth is returned by suction while the tube remains in the jejunum but only about one-third after it reaches the distal ileum. With the tube in the ileum it is usually unnecessary to give supplementary parenteral fluids.

The progress of the tube is followed by daily roentgenograms of the abdomen or short fluoroscopic examinations. When an obstruction is encountered, the nature and location of the lesion is studied by injecting 50 to 100 cc. of barium suspension under fluoroscopic control. The tube is never removed until it has reached the point of obstruction in the small bowel, or until it has reached the cecum, even though the patient may be markedly improved clinically. This last point is very important, for many patients are completely relieved of symptoms after 24 hours of gastric or small intestinal suction, particularly in mechanical obstructions, where the vigorous peristalsis proximal to the point of obstruction causes a rapid reflux of the contents in the obstructed loops which can be evacuated by the tube far above the point of obstruction. However, unless the tube is allowed to advance, the nature and position of the lesion cannot be determined. Too often the tube has been removed because the patient was symptomless except for mild discomfort in the nose and throat, only to have the ileus recur, requiring a second intubation, always more difficult than the first. In cases with mechanical obstructions, even in the terminal ileum, the balloon may be passed to the point of obstruc-

tion within 24 to 36 hours, but in those with a paralytic ileus three to five days may be required to reach the cecum.

Occasionally gastric distention persists after the tube has passed beyond the stomach and is controlling the small bowel distention. A gastric lavage may be necessary for a day or so in addition to the Miller-Abbott suction. Particularly is it advisable to lavage the stomach before operations. A few cases have presented mild gastric distention at exploration in spite of the completely collapsed small bowel.

Report of Cases.—Our cases can be roughly divided into three clinical groups: (1) Noninflammatory obstructions: A. Paralytic type. B. Mechanical type. (2) Obstructions with peritonitis. (3) Obstructions with gangrene of bowel.

Groups 1 and 2 are discussed separately, as the presence of peritonitis with obstruction places them apart as especially difficult problems in intubation. The cases suspected of gangrene of the bowel are, of course, subjected to immediate operation and the tube used only in the short preoperative period while fluids are administered, and for the postoperative distention, if it occurs.

The distinction is made between "postoperative distention" and "postoperative ileus" by the response of each case to our previous routine treatment. We have reserved the term "postoperative ileus" for those cases with clinical distention that are not relieved within two or more days by prostigmin or pitressin, poultices and rectal treatments, and duodenal or gastric suction. Moreover, these cases have evidence of distended loops of small bowel with fluid level formation as seen radiographically. Any later reference to "routine treatment" in this paper implies that the various procedures mentioned here had been tried before intubation. In recent months the Miller-Abbott tube has been used prophylactically in many cases with mild postoperative distention which disappeared after 12 to 24 hours of gastric or upper small bowel suction, but these cases are not included in this report. All cases reported in this series faced exploration or enterostomy prior to intubation.

GROUP 1: *Noninflammatory Obstructions.*—A. Paralytic Type: Twelve cases which were treated in this group are listed in Table I. The immediate problem in these cases was one of maintaining the patient until distention was controlled and a diagnosis made without exploration.

CASE REPORTS—GROUP 1A

Case 1.—P. H., No. 366,942 (Fig. 2): A male, age 59, developed bronchopneumonia in both lower lobes. There was a persistent ileus after ten days of routine treatment. A Miller-Abbott tube was passed into the duodenum on the eleventh hospital day, and deflation was complete after 36 hours. At that time the tip of the Miller-Abbott tube was shown, by fluoroscopic examination, to be at the cecum. The tube was removed and recovery was uneventful.

Case 2.—N. I., No. 39,152: A male, age 59, with a transverse myelitis due to neuromyelitis optica, had marked ileus for ten days without relief by routine treatment. The Miller-Abbott tube required seven days to completely deflate the small bowel and reach the cecum, but distention again appeared in the upper jejunum. The tube was withdrawn

TABLE I

NONINFLAMMATORY OBSTRUCTIONS

Paralytic Type

Case No.	Hospital No.	Age	Cause of Obstruction	Time Required for Miller-Abbott Treatment						Result
				Duration of Ileus	Control Symptoms	To Pass Pylorus	X-Ray Guidance necessary	Reach Cecum	Total Time	
				Days	Hours	Hours		Days	Days	
1	P. H. No. 366,942	59	Bronchopneumonia	10	6	3	No	2	2	Recovered
2	N. I. No. 39,152	59	Transverse myelitis due to neuromyelitis optica	10	12	24	No	7	18	Recovered
3	P. H. No. 547,451	58	Postoperative herniorraphy. Spinal pontocain	4	24	6	Yes	6	6	Recovered
4	P. H. No. 76,608	32	Postoperative exploratory celiotomy	4	12	12	Yes	4	4	Recovered
5	P. H. No. 421,513	63	Postoperative cecorraphy and cecopexy	6	12	8	No	5	5	Recovered
6	P. H. No. 548,256	29	Postoperative celiotomy for division of adhesions	5	12	6	No	3	3	Recovered
7	P. H. No. 571,349	53	Postoperative hysterectomy	9	10	8	No	3	3	Recovered
8	P. H. No. 533,358	35	Postoperative suspension of uterus	4	48	6	Yes	5	6	Recovered
9	P. H. No. 577,860	55	Postoperative colostomy—first stage abdominoperineal resection	3	48	36	Yes	4	4	Recovered
10	P. H. No. 571,830	60	Postoperative—one-stage abdominoperineal resection	3	48	48	No	6	6	Recovered
11	P. H. No. 440,306	60	Postoperative partial colectomy. Generalized edema	7	48	4	No	5	6	Recovered
12	P. H. No. 564,231	60	Ureteral calculus	4	4	1	Yes	6 hrs. before and 2 days after exploration		Recovered

to the duodenum and allowed to traverse the small bowel again. The neurologic symptoms gradually disappeared during this period and the tube was removed after 18 days of continuous suction. Recovery was slow but uneventful.

Case 3.—P. H., No. 547,451: A male, age 58, developed severe ileus after a herniorraphy, performed under spinal anesthesia (20 mg. pontocaine in third lumbar space). The Miller-Abbott tube was passed on the fifth postoperative day after routine treatment had failed for three days. The barium studies on the eighth postoperative day showed dilated loops of ileum distal to the advancing tip of the tube. The cecum was reached on the ninth postoperative day and the tube removed. Recovery was uneventful.

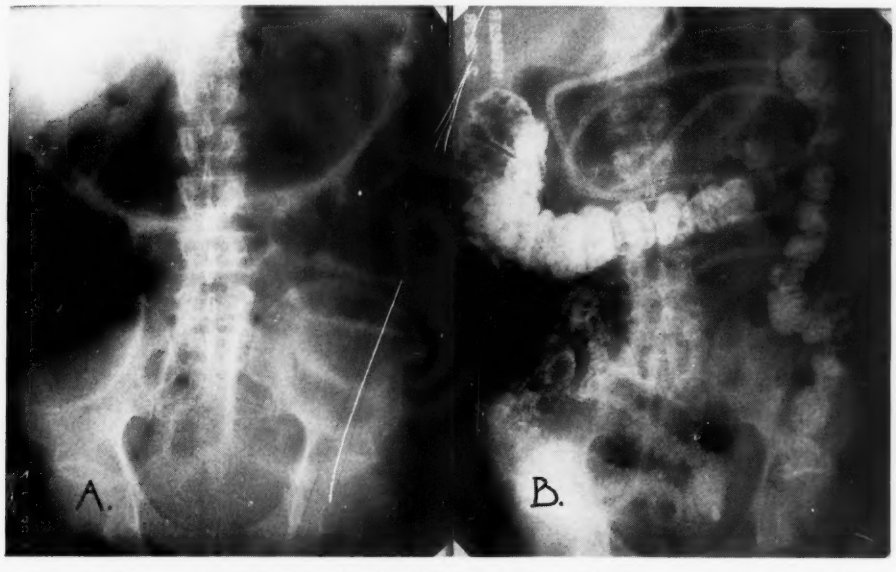

FIG. 2.—Case 1.: Bronchopneumonia with Paralytic Ileus. (A) Plain roentgenogram of abdomen showing distention prior to intubation. (B) After deflation with the Miller-Abbott tube. Barium injected through the tube shows an unobstructed bowel.

Cases 4 to **10,** inclusive, had marked ileus following various surgical procedures. All were cured by one deflation with the Miller-Abbott tube after routine measures had failed.

Case 11.—P. H., No. 440,306: A female, age 60, developed severe ileus after the resection of the sigmoid, end-to-end anastomosis, for carcinoma. Twenty liters of parenteral fluids were administrated during the first five postoperative days. Generalized edema and ascites developed on the fourth postoperative day. Blood studies showed a high hematocrit (54 per cent) and a low serum protein (4.2 Gm. per cent). Cecostomy, performed on the fifth postoperative day, failed to function. Transfusions were helpful but failed to correct the abnormal fluid balance. The Miller-Abbott tube was passed into the upper jejunum on the seventh postoperative day and delivered large quantities (11 liters) of fluid during the first 48 hours, relieving the patient of nausea and vomiting. Routine treatments had failed prior to intubation. Roentgenograms of the abdomen at this time, however, showed many dilated loops of ileum distal to the advancing tip of the tube. The Miller-Abbott tube reached the cecum after five days of continuous suction, and the cecostomy began to function satisfactorily for the first time. Both the Miller-Abbott and cecostomy tubes were removed on the thirteenth postoperative day, when a barium suspension, injected through the Miller-Abbott tube, passed into the rectum after one hour. Recovery was uneventful.

TABLE II

NONINFLAMMATORY OBSTRUCTIONS

Mechanical Type

Case No.	Age	Cause of Obstruction	Time Required for Miller-Abbott Treatment					Operations for Ileus	Result
			Duration of Ileus	Control Symptoms	To Pass Pylorus	To Reach Obstruction	Total Time		
			Days	Hours	Hours	Days	Days		
13 to 18 incl.	43 20–58	Early postoperative adhesions *	5.2 (4–7)	22.7 (12–48)	19.0 (6–48)	3.0 (2–4)	8.0 (6–10)	3	All recovered
19 & 20	45 & 27	Nonfunctioning ileocolostomy after resection of cecum	3 & 4	6 & 8	12 & 20	4 & 5	6 & 10	None	Both recovered
21 to 44 incl.	47.8 14–70	Late postoperative adhesions,† 2 Mos. to 19 yrs. after original abdominal operation	5.4 (3–30)	29.2 (4–48)	15.3 (1–60)	3.25 (2–5)	8.6 (4–21)	18	All recovered
45	38	Incarcerated pelvia hernia after resection of coccyx	2	12	4	Not demonstrated	2	No	Recovered
46	54	Lymphosarcoma of ileum	2	12	3	1	4	Yes	Recovered
47	60	Volvulus of cecum	3	12	2	12 hrs.	7	Yes	Recovered
48	13	Intussusception—lymphosarcoma of ileum	21	12	6	4	7	Yes	Recovered
49	65	Carcinoma of ovary invading ileum	12	24	12	4	7	Yes	Recovered
50	59	Carcinoma of sigmoid invading ileum	14	48	24	5	9	Yes	Died P.O. Pneumonia

* Early postoperative adhesions followed two hysterectomies, two appendicectomies, one abdominoperineal resection and one exploration for division of late postoperative adhesions two years after hysterectomy.

† Late postoperative adhesions followed 12 hysterectomies, five appendicectomies, two colostomies, one partial colectomy (sigmoid), one cesarian section, one marsupialization of ovarian cyst and one nephrectomy and ileostomy. Five of these cases had multiple operations (2 to 10). One case was considered a failure because the patient was hysterical after six hours of intubation and the tube was removed before operation, without localizing the lesion.

Fluoroscopy was employed in 26 of the 38 cases.

Hospital Numbers for Cases 13 to 50 inclusive: P. H. 559,621, P. H. 523,378, P. H. 235,467, P. H. 569,465, P. H. 578,634, P. H. 423,893, P. H. 513,557, P. H. 566,772, P. H. 433,379, P. H. 316,569, P. H. 532,728, P. H. 534,356, P. H. 555,755, P. H. 169,106, P. H. 225,460, P. H. 421,489, P. H. 393,502, P. H. 571,319, P. H. 564,154, P. H. 543,573, P. H. 466,386, P. H. 379,773, P. H. 528,402, P. H. 313,032, P. H. 589,165, P. H. 364,304, P. H. 316,569, P. H. 78,700, P. H. 375,309, P. H. 325,422, P. H. 508,322, P. H. 338,808, P. H. 322,123, P. H. 576,668, P. H. 525,422, P. H. 545,413, P. H. 550,180, P. H. 556,576.

Case 12.—P. H., No. 564, 321: A male, age 60, had had increasing ileus with crampy, colicky pains in the right lower quadrant for four days before admission. An apendicectomy with drainage had been performed 15 years previously. Intubation was started and deflation was progressing satisfactorily but repeated blood counts showed an increasing white blood count, making exploration advisable for diagnosis. At exploration, the small bowel had been deflated and no cause for the ileus was found. Later roentgenograms of the abdomen showed a right ureteral calculus which had completely blocked the right ureter, accounting for the negative uranalysis done on admission. The tube was removed two days after exploration and recovery was uneventful.

GROUP 1: *Noninflammatory Obstructions.*—B. Mechanical Type: The 38 cases of mechanical obstructions have been mostly early and late postoperative adhesions. The other causes are listed in Table II. Many cases due to late postoperative adhesions were seen early without marked distention or dehydration, and any cases with an obvious hernia causing the obstruction have been subjected to immediate operation, without preliminary deflation, and are not included in this report. One death occurred in this group, due to postoperative pneumonia rather than ileus.

CASE REPORTS—GROUP IB

Case 13.—P. H., No. 559,267 (Fig. 3): Early Postoperative Adhesions: A female, age 58, developed increasing ileus for four days after a hysterectomy, in spite of routine treatment. The Miller-Abbott tube was passed on the fourth postoperative day and distention was completely relieved within 24 hours, although the abdominal roentgenograms showed the balloon still in the stomach. Intubation was continued, however, and the forward progress of the balloon was arrested in the left lower quadrant on the seventh postoperative day. Barium injected through the Miller-Abbott tube demonstrated an angulation of the ileum. The lesion was again demonstrated on the twelfth postoperative day, while the patient had remained symptom free on continuous suction and a low residue diet. Because the barium injected through the tube had been recovered in the stools, the surgeon elected to remove the tube without exploration. Distention recurred and nausea and vomiting again began on the sixteenth postoperative day. A second intubation was instituted and exploration showed the adhesion constricting the ileum in the pelvis at the position previously demonstrated by the roentgenologic studies. The tube was removed three days later, after the patient had had a normal bowel movement. Recovery was uneventful.

Cases 19 and **20.**—Nonfunctioning Ileotransverse Colostomy. Both of these cases, after resections of the cecum, developed severe ileus, apparently from edema at the site of anastomosis. Barium injected through the tube before removal demonstrated the patency of the bowel lumen and both cases made uneventful recoveries.

Case 21.—P. H., No. 433,379 (Fig. 4): Late Postoperative Adhesions: A female, age 47, had had repeated attacks of crampy abdominal pains, nausea and vomiting with distention for two years following the repair of a postoperative ventral hernia. All previous attacks had subsided spontaneously, but the present attack had continued for four days before admission. Deflation was accomplished with the Miller-Abbott tube after 48 hours of continuous suction. Barium studies demonstrated the point of angulation of the bowel beneath the old midline scar. The adhesions were divided without difficulty at exploration. The Miller-Abbott tube had advanced through numerous adhesions to within two feet of the ileocecal valve. Only the adhesions distal to the tip of the tube were divided. The tube was removed on the fourth postoperative day and recovery was uneventful.

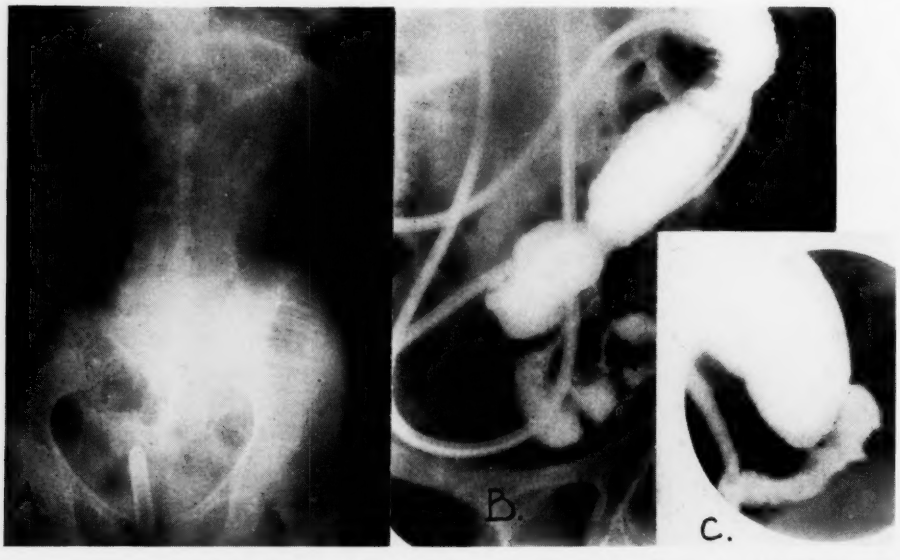

FIG. 3.—Case 13: Mechanical Ileus Due to Early Postoperative Adhesions. (A) Abdominal roentgenogram showing distention of small bowel four days after hysterectomy. (B) The arrow shows the point of constriction in a partially deflated loop of ileum with the tip of the Miller-Abbott tube overriding the adhesion. (C) A pressure roentgenogram showing the point of constriction uncovered and in profile.

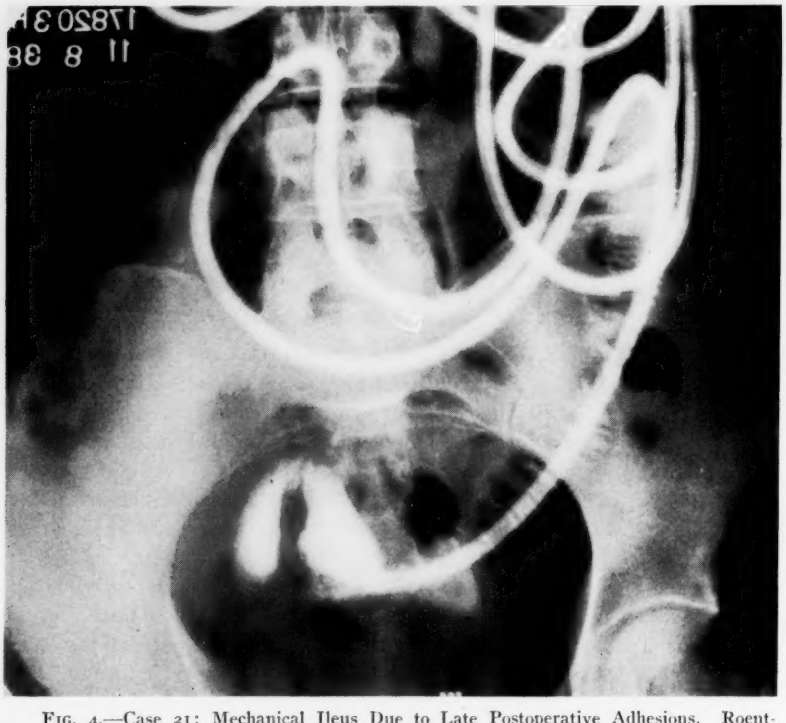

FIG. 4.—Case 21: Mechanical Ileus Due to Late Postoperative Adhesions. Roentgenogram of the abdomen 48 hours after intubation. Barium injected through the Miller-Abbott tube showing a partially deflated loop of ileum attached beneath a two-year-old lower right rectus scar.

Case 44.—P. H., No. 338,808: Late Postoperative Adhesions Requiring Prolonged Preoperative Preparation: A female, age 70, had been followed for 15 years because of recurrent attacks of distention, nausea and vomiting which had subsided spontaneously on a liquid diet. The present attack had lasted for one month and the patient was extremely emaciated and dehydrated. Deflation with the Miller-Abbott tube required seven days. A high protein-low residue diet was started on the fifth hospital day, and the patient gained approximately ten pounds in weight before operation on the eighteenth hospital day. Parenteral liver and fluids, intravenous vitamins, and two blood transfusions were administered in addition to the food by mouth. At exploration, no free peritoneal cavity was encountered in the right lower quadrant and only an ileostomy was accomplished. The patient has been fairly comfortable for 12 months and has gained weight. An ileocolostomy will be attempted later.

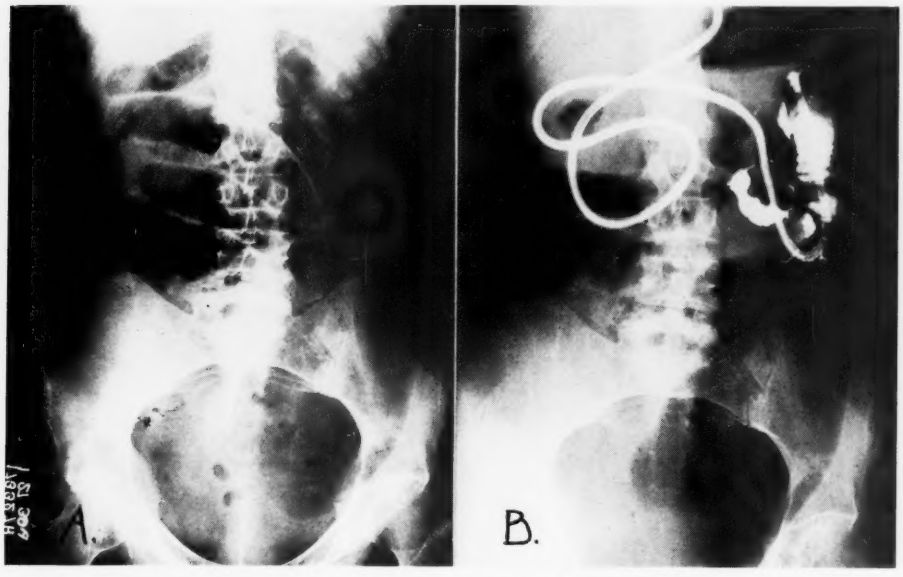

FIG. 5.—Case 47: Volvulus of Ileum and Cecum. (A) Abdominal roentgenogram showing distention of small bowel, with an isolated loop in the left lower quadrant which did not deflate after 12 hours of small bowel suction with the Miller-Abbott tube. (B) This suggested a double obstruction, as in a volvulus, which was confirmed at operation.

Case 45.—P. H., No. 322,123: Incarcerated Pelvic Hernia: The importance of examining all previous operative scars is illustrated in this case. A female, age 40, had suffered from recurring attacks of distention for three years. Seven years previously, the coccyx had been resected for a sarcoma. All previous attacks of distention had subsided spontaneously, but the present ileus had continued for two days before admission. Deflation was easily accomplished with the Miller-Abbott tube and the tip reached the cecum on the second hospital day without demonstrating the cause of the obstruction. A barium enema was negative. A small intestine study was started after the removal of the Miller-Abbott tube. The patient accidentally coughed during the fluoroscopic examination and barium-filled loops were observed to protrude through the pelvic floor into the region of the old operative scar. A pelvic hernia was confirmed and repaired at later operation.

Case 47.—P. H., No. 525,413 (Fig. 5): Volvulus of Cecum: A female, age 60, was admitted to the hospital, complaining of distention, nausea and vomiting of three days' duration. A hysterectomy had been performed three years previously, for what was said to have been a fibromyoma of the uterus. One year later, a firm mass was removed from the operative scar which proved to be carcinoma, presumably an implantation from the

previous operation. No previous attacks of distention had occurred. Intubation was started on admission, and the dilated loops of small bowel disappeared within 12 hours, but a palpable, isolated loop of distended bowel remained in the left lower quadrant. Exploration was advised by the radiologist and showed a large redundant cecum which was involved in a volvulus together with the terminal ileum. The twist was corrected and a cecostomy performed to anchor the cecum in the right lower quadrant. The tube

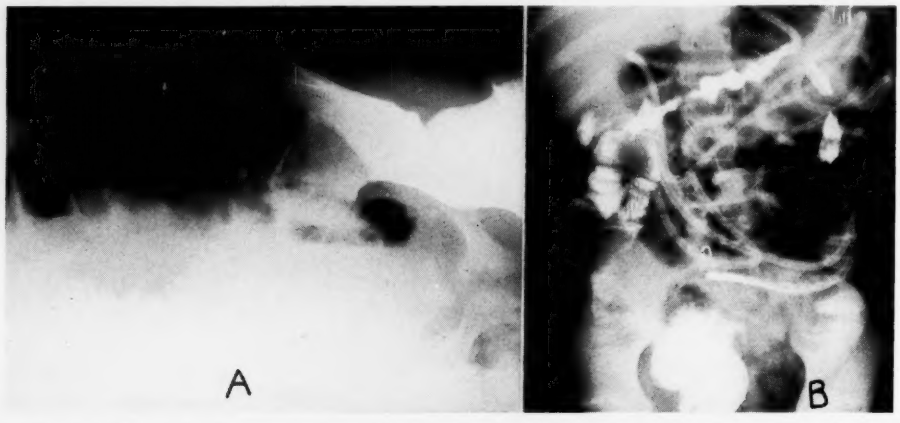

FIG. 6.—Case 48: Intussusception. (A) Lateral decubitus, abdominal roentgenogram showing marked distention of the small bowel with fluid level formation. (B) Plain roentgenogram, four days later, after deflation with the Miller-Abbott tube. Barium injected through the tube demonstrates an intussusception of terminal ileum into cecum and ascending colon.

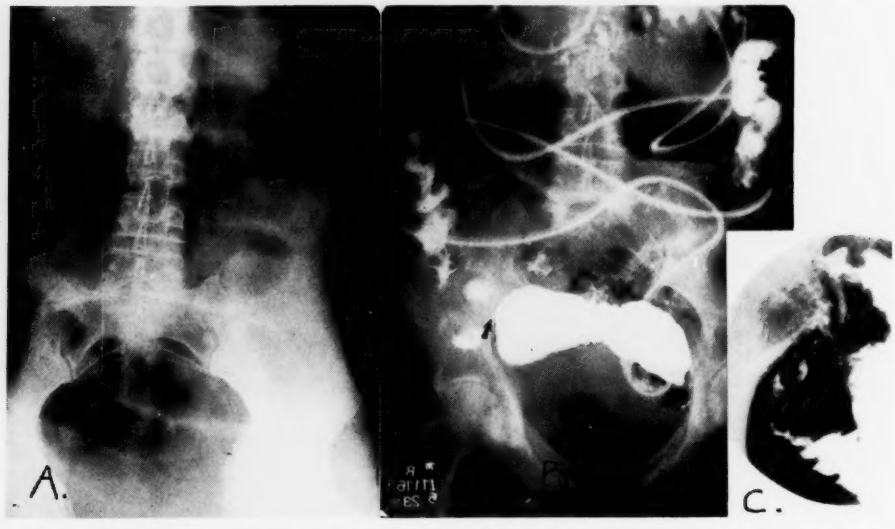

FIG. 7.—Case 49: Carcinoma of Ovary Involving Ileum. (A) Abdominal roentgenogram showing small bowel distention. (B) After deflation with the Miller-Abbott tube showing dilated loop of ileum proximal to point of obstruction. (C) A pressure roentgenogram of the constricted lumen suggests that a mass is present within the wall of the bowel.

was removed on the fifth postoperative day, when barium injected showed a patent terminal ileum and cecum. Recovery was uneventful.

Case 48.—P. H., No. 545,242 (Fig. 6): Intussusception: A male, age 13, was admitted for crampy, right lower quadrant pain, distention and melena of three weeks' duration. Distention and dehydration were marked, and a questionable mass could be palpated in the right lower quadrant. The Miller-Abbott tube was used for deflation,

while fluids and food were administered. Barium studies demonstrated an intussusception of the terminal ileum into the cecum after the patient had been greatly improved by four days of treatment. At operation, a resection was found to be necessary, and the tube was left in place for two days after operation. The mass in the bowel lumen proved to be a lymphosarcoma. The patient recovered from the immediate operation and was given extensive radiation but died six months later of generalized lymphosarcoma.

Case 49.—P. H., No. 550,184 (Fig. 7): Carcinoma of Ovary Invading Terminal Ileum: An emaciated female, age 65, complained of recurrent attacks of distention, fever, and questionable melena following an appendicectomy for a normal appendix 16 months previously. The symptoms antedated the operation by two months and had continued with increasing severity. Deflation with the Miller-Abbott tube required five days, at which time roentgenologic examination showed an obstruction of the terminal ileum, thought to be due to a neoplasm, since a filling defect could be seen in the wall of the bowel. At operation, a carcinoma of the right ovary was found invading and obstructing the terminal ileum. Ileotransverse colostomy was performed, without resection of the widespread tumor. The patient has remained symptomless and gained 20 pounds during the ten months following operation.

COMMENT.—In cases with simple mechanical or paralytic ileus the Miller-Abbott method has made immediate operation unnecessary. Surgical treatment can be instituted after an accurate diagnosis is made, and the patient's condition greatly improved. Heretofore, it has been of little value to give barium by mouth to demonstrate the exact nature and the site of an obstruction in the presence of ileus, since without deflation, the barium will not reach the point of obstruction or will be so diluted by fluid as to be practically useless. Now, however, with deflation the exact site of the obstruction can be studied by barium injected through the tube and withdrawn later if desired. The movements of the balloon as it attempts to pass an obstruction give valuable information when observed fluoroscopically. Roentgenograms, made with a compression device,[20] may bring a point of obstruction into profile which would otherwise not be visualized, since there is often a tendency of the tip of the tube to override the site of obstruction in the barium filled loop just proximal to it (Fig. 3C). In the early postoperative cases, the intubation settled the difficult question as to whether the ileus was paralytic or mechanical in nature.

The patients with long-standing mechanical obstructions are usually in very poor condition when admitted. Protein foods can be given by mouth as deflation proceeds, and are far more effective than transfusions in restoring the low serum proteins often encountered in these cases. In less serious cases several explorations were avoided. However, when surgery is indicated, the location and often the nature of the lesion were known before entering the abdomen. The surgeon is also aided by having the tube to act as a guide, particularly when generalized adhesions are present. The resection of a pathologic bowel loop is made easier by reducing the size of the distended proximal loop by the preliminary deflation. The tube is left in place proximal to the anastomosis, with the balloon deflated, to control postoperative distention, which protects the suture line from disruption. The vital importance of

TABLE III

OBSTRUCTIONS WITH PERITONITIS

Miller-Abbott Tube Passed into Small Bowel

Case No.	Hospital No.	Age	Cause of Obstruction	Duration of Ileus	Mechanical Obstruction Demonstrated	Operation for Obstruction	Time Required for Miller-Abbott Treatment			Result
							To Pass Pylorus Hours	X-Ray Guidance	Total Time Days	
51	P. H. No. 328,925	40	Diffusing peritonitis, probably due to pneumococcus	2	No	No	6	Yes	7	Recovered
52	P. H. No. 506,110	22	Gangrene of appendix, with abscess. Localized peritonitis	2	No	No	12	No	4	Recovered
53	P. H. No. 568,465	49	Acute appendicitis. Diffusing peritonitis	2	No	No	24	No	3	Recovered
54	P. H. No. 369,231	70	Localized peritonitis, after cecostomy	3	No	No	24	No	5	Recovered
55	P. H. No. 576,826	51	Acute diverticulitis, with localized abscess	3	Yes	No	24	Yes	4	Recovered
56	P. H. No. 375,470	38	Acute appendicitis, with diffusing peritonitis	3	No	No	48	No	8	Recovered
57	P. H. No. 558,220	32	Acute appendicitis, with diffusing peritonitis	3	No	No	24	No	3	Recovered
58	P. H. No. 442,467	61	Acute cholecystitis, with localized peritonitis	3	No	No	24	No	4	Recovered
59	P. H. No. 566,943	14	Acute appendicitis, with generalized peritonitis	4	Yes	No	72	No	10	Recovered
60	P. H. No. 570,936	13	Acute appendicitis, with localized peritonitis	4	Yes	No	4	Yes	12	Recovered
61	P. H. No. 580,822	51	Gangrene of appendix, with abscess. Localized peritonitis	5	Yes	No	3	No	7	Recovered
62	P. H. No. 563,298	17	Gangrene of appendix, with generalized peritonitis	9	Yes	Yes	72	Yes	41	Recovered
63	P. H. No. 541,310	37	Generalized peritonitis. Purpura. Sepsis of unknown origin	10	Yes	Yes	24	Yes	19	Died
64	P. H. No. 560,491	39	Acute appendicitis, with localized peritonitis	11	Yes	No	6	Yes	5	Recovered

eliminating tension on the suture line by keeping the bowel collapsed cannot be overemphasized.

It is of interest that none of these cases, or the ones observed by Abbott,[17] showed a complete obstruction of the bowel lumen when, after deflation, barium was injected by means of the tube. Although the radiopaque material could always be seen to pass through the partially occluded lumen, this could not be taken as evidence that the obstruction would not again be complete when distention recurs and causes further kinking of a fixed loop. All the cases in this group which failed to allow the passage of the tube or a small balloon at a certain point after several days of continuous suction and in which an angulated segment could be repeatedly demonstrated roentgenologically, required surgery. In the inflammatory group, however, deflation often relieved the obstruction without allowing the tube to progress.

GROUP 2: *Obstructions with Peritonitis.*—In the cases where the ileus is complicated by an inflammatory process involving the peritoneal cavity, whether the ileus be paralytic, mechanical or both, a special problem arises in intubation, which group will be reported in detail later. In this report, we only wish to show, by the accompanying tables, the type of case treated and the importance of early intubation, which is emphasized by observing the time relation between the duration of the ileus and the formation of mechanical obstructions.

The term "generalized peritonitis" is used only in those cases proved to have multiple abscesses by secondary operation or at autopsy. On the other hand, the term "diffusing peritonitis" is used to designate those cases with clinical signs of widespread peritonitis either at or after operation but where the widespread peritonitis was not confirmed by secondary operation or at autopsy.

Case 56.—P. H., No. 328,925 (Fig. 8): A female, age 40, had signs of generalized peritoneal irritation following four days' illness beginning as an acute upper respiratory infection accompanied by generalized aching pains and temperature ranging between 102° and 103.6° F. When admitted on the fifth day of her illness, she complained of increasing distention and colicky abdominal pains, not localized, which had begun six hours previously. The lungs were clear and remained so. A throat culture showed on smear what was thought to be a pneumococcus but this was not substantiated by culture. Sulfapyridine, given (7 Gm.) for 24 hours, caused a dramatic fall to normal of both temperature and pulse, but the drug was discontinued because of nausea and vomiting. The ileus continued to increase for two days in spite of vigorous routine measures. The Miller-Abbott intubation was started on the third hospital day. Decompression was slow, but tenderness and pain disappeared as each segment of bowel was deflated. Sulfapyridine was again started on the fourth hospital day, due to a return of elevated temperature and pulse rate, and again there was a dramatic fall to normal. The tube was temporarily arrested in the right lower quadrant and an indefinite tender mass suggesting matted loops of distended bowel could be palpated in the region of an undeflated loop seen in the roentgenogram. All abdominal signs disappeared on the tenth hospital day, and barium, injected through the tube, passed rapidly into the cecum. The tube was removed after a one-day trial without suction. The sulfapyridine was injected as a suspension through the tube into the ileum when started the second time and suction discontinued for only 15 minutes after each

injection. A blood concentration of 5 mg. per cent was found after 6 Gm. of the drug had been administered in that manner. Recovery was slow but uneventful.

Case 60.—P. H., No. 570,936 (Fig. 9): A female, age 13, showed increasing distention two days after an appendicectomy with drainage, for acute appendicitis with perforation and localized peritonitis. The Miller-Abbott intubation was started on the second postoperative day, at which time she was desperately ill with marked distention

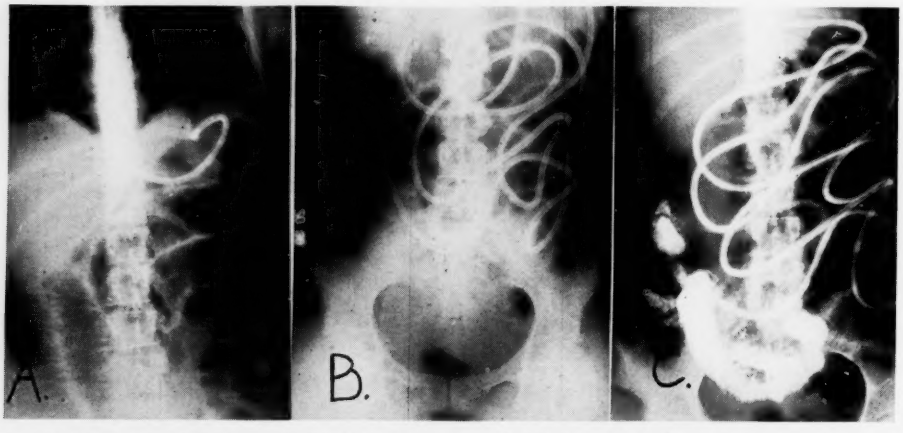

FIG. 8.—Case 56: Primary Peritonitis with Ileus. (A) Plain roentgenogram of abdomen after 24 hours of continuous gastric suction showing persistent distention of small bowel. (B) Three days later, the Miller-Abbott tube is arrested in the lower ileum with persistent distention distal to the tip of the tube. (C) Five days after (A), the small bowel is completely deflated and barium injected through the tube passes into the cecum.

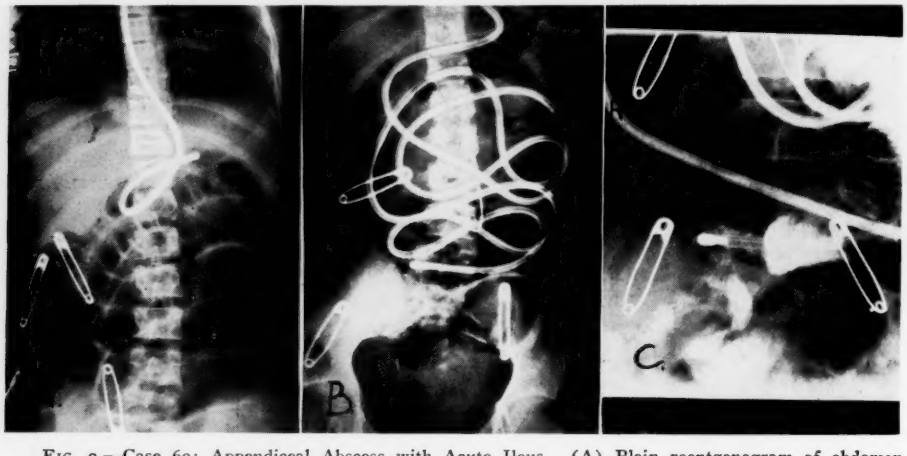

FIG. 9.—Case 60: Appendiceal Abscess with Acute Ileus. (A) Plain roentgenogram of abdomen showing the Miller-Abbott tube in the stomach after 24 hours of gastric suction. The small bowel is still distended. (B) The tube arrested in the region of the appendiceal abscess, two days later. (C) Barium injected shows angulation with partial obstruction of the bowel. The obstruction disappeared after the infection subsided.

and fecal vomiting. The bowel was rapidly deflated after 48 hours, and fluids were thereafter given orally. A constriction in the bowel lumen was demonstrated in the terminal ileum on the fourth postoperative day. This was thought to be due to an angulation of the bowel by adhesions at the site of the residual right lower quadrant abscess. Distention was controlled by continuous suction above the site of obstruction until the patient had a normal stool on the twelfth postoperative day. During this time, the oral intake had been increased to include a low residue diet. The tube was removed on the sixteenth post-

operative day, after suction had been discontinued for four days without recurrence of the distention. Recovery was uneventful.

Case 62.—P. H., No. 563,298 (Fig. 10) : A male, age 17, was admitted gravely ill with generalized peritonitis. His history suggested the rupture of an acute appendix five days previously. On admission the Miller-Abbott tube was introduced into the stomach and continuous suction maintained thereafter. The patient received nine liters of fluid and blood during the first 24 hours before an adequate fluid balance could be obtained. At the end of this time, the right lower quadrant was opened and drained under local anesthesia but no attempt was made to remove the appendix. The patient's serious condition pre-

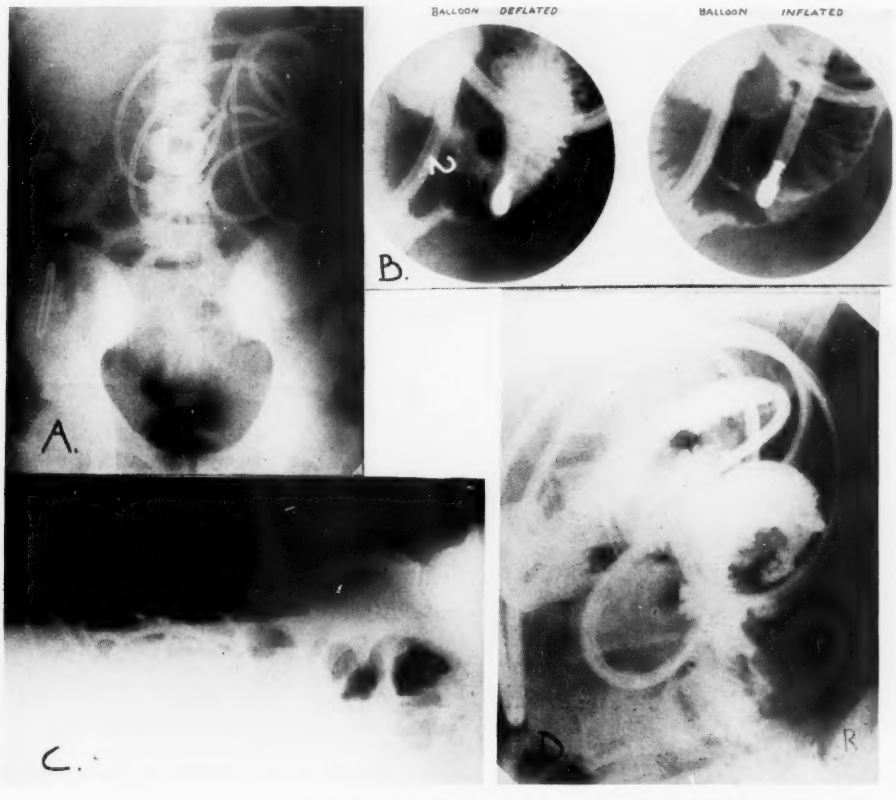

FIG. 10.—Case 62: Generalized Peritonitis with Acute Ileus. Plain roentgenogram of abdomen on the eleventh hospital day showing the Miller-Abbott tube arrested in the left lower quadrant. (B) Pressure roentgenogram at the point of obstruction after barium was injected through the tube. On the left, the balloon is deflated and on the right, the balloon is inflated. (C) Four days later, after two days without continuous suction the small bowel distention has recurred and the lateral decubitus, abdominal roentgenogram shows the Miller-Abbott tube within the distended loops of ileum and jejunum. (D) A lateral abdominal roentgenogram to localize the point of obstruction before operation to release the adhesion.

vented fluoroscopic examination, hence the tube did not reach the duodenum until the fifth hospital day. Rapid deflation of the upper small bowel was accomplished thereafter, allowing the patient to take food and fluids by mouth. A second abscess, in the right upper quadrant, was drained on the ninth hospital day. The tip of the tube was shown to have stopped in the left lower quadrant and would not advance after several days of continuous suction. Barium studies on the eleventh hospital day demonstrated a partial obstruction of the ileum, thought to be caused by an angulation of the bowel by adhesions. These observations were confirmed by repeated examinations on the seventeenth and twenty-fifth hospital days. With continuous suction maintained, the patient was symptomless on a low

TABLE IV

OBSTRUCTIONS WITH PERITONITIS

Miller-Abbott Tube Failed to Reach the Small Bowel

Case No.	Hospital No.	Age	Cause of Obstruction	Duration of Ileus	Mechanical Obstruction Demonstrated	Operation for Ileus	Time Allowed to Pass Pylorus	Fluoroscopic Guidance Allowed	Result
				Days			Hours		
65	P. H. No. 532,728	14	Acute appendicitis, with generalized peritonitis	4	Yes	Ileostomy	48	Yes	Died
66	P. H. No. 374,518	41	Generalized peritonitis, after repair of cystocele	4	No	Ileostomy	48	Yes	Died
67	P. H. No. 249,200	64	Retroperitoneal abscess, after resection of cecum for Ca. of cecum. Diffusing peritonitis	5	No	Ileostomy	6	Yes	Died
68	P. H. No. 537,264	51	Acute appendicitis, with abscess. Localized peritonitis	6	Yes	Ileostomy	8	No	Recovered
69	P. H. No. 552,089	51	Acute diverticulitis, with abscess. Generalized peritonitis	7	Yes	Cecostomy Ileostomy	12	Yes	Died
70	P. H. No. 527,792	48	Generalized peritonitis. Paratyphoid liver abscess	14	Yes	Ileostomy	24	Yes	Died
71	P. H. No. 541,231	25	Acute appendicitis, with generalized peritonitis	14	Yes	Ileostomy	24	Yes	Died

residue diet and supplementary parenteral fluids were not required. The patient was tried without suction on the fifteenth day and again on the twenty-third day, but each time developed a recurrence of the ileus. Roentgenograms of the abdomen, made during the second trial two days after suction had been discontinued, showed the tube within distended loops of small bowel with fluid level formation in the lateral position. The partial obstruction was released by operation on the thirty-first hospital day. Fibrous adhesions were widespread, and it would have been practically impossible to locate the point of obstruction without the tube to guide the surgeon. Continuous suction was maintained until the thirty-sixth hospital day when rectal treatments returned a fairly normal stool. Suction was discontinued thereafter, and the tube removed on the forty-first hospital day. Appendicectomy was performed 20 days later (the sixty-first hospital day). The patient eventually recovered after a long convalescence. No complication could be ascribed to the long intubation and, surprisingly enough, after the first two weeks, the patient tolerated the tube without complaint.

Case 64.—P. H., No. 541,310: The one death in this group occurred in a male, age 37, who was admitted as "Henoch's purpura," after two weeks of septic temperature, purpuric manifestations and increasing distention. The ileus was severe on admission but responded promptly to Miller-Abbott intubation. Repeatedly, blood, stool, throat and sputum cultures failed to identify the organism. Blood agglutination studies were not significant. The Miller-Abbott tube controlled the ileus over a period of 18 days, but the septic temperature continued. An exploratory celiotomy, on the eighth hospital day, showed a few adhesions beneath an old right rectus scar, but the ileus was due to a widespread inflammatory process. Culture of the peritoneal exudate gave no growth. An ileostomy was performed but did not function when the Miller-Abbott suction was discontinued. The tube was withdrawn to the upper jejunum on three occasions and allowed to traverse and deflate the small bowel. Purpuric manifestations continued and the patient complained so bitterly of the tube that it was removed on the eighteenth hospital day. He died in shock two days later after a rectal treatment returned large quantities of bright red blood.

CASE REPORTS—GROUP 2

Case 65.—P. H., No. 532,729: A poorly nourished girl, age 14, developed an acute ileus with peritonitis following appendicectomy without drainage for acute appendicitis. Cultures of the peritoneal exudate showed a hemolytic streptococcus and *B. coli*. The Miller-Abbott tube passed into the third portion of the duodenum four days after operation, but the infected and edematous bowel was apparently powerless to advance the tube. An ileostomy, performed on the sixth postoperative day, did not function, and the patient died 12 hours later.

Case 66.—P. H., No. 374,518: A widespread hemolytic streptococcus peritonitis followed a cystocele repair in a female, age 41. When first seen four days after operation, the patient was markedly distended and vomiting fecal fluid. The surgeon reported that one of the sutures might have entered the peritoneal cavity and the possibility of a compromised loop of bowel made exploration appear the logical procedure, but the patient refused a second operation. The Miller-Abbott tube was placed at the pylorus under fluoroscopic guidance three times during the next two days, only to have it removed by the patient in spite of special precautions. Operation was finally accepted on the sixth postoperative day, at which time ileostomy was performed, which, however, failed to function and the patient died 24 hours later.

Cases 54 and **70** were moribund when seen. Both had widespread peritoneal infection, and very little time was spent attempting to pass the tube. Ileostomy failed to function in either case.

Case 69 was in good condition when first seen. The obstruction was caused by a large pelvic abscess due to a perforation of the sigmoid following acute diverticulitis. Roentgenograms, 24 hours after intubation, showed the tip of the tube in the upper

jejunum with all distention apparently confined to the large bowel. A cecostomy was performed, and the patient's abdomen became soft within three hours. At operation, no dilated small bowel was seen, hence the Miller-Abbott tube was removed. He developed a recurrence of small intestinal distention and a second intubation could not be accomplished. An ileostomy failed to deflate the small bowel. The patient died of generalized peritonitis, with distention of the small bowel and bilateral pneumonia, two days after the second operation. Autopsy showed multiple points of obstruction in the ileum as well as the sigmoid. The small bowel obstruction would have been demonstrated if the Miller-Abbott tube had been allowed to continue downward at the first intubation.

Case 71.—P. H., No. 541,231: A female, age 25, was admitted with a generalized peritonitis following acute appendicitis. Appendicectomy with drainage was performed on admission. Distention was fairly well controlled with duodenal suction until the eleventh hospital day, when routine methods gave no relief. The continual drain of electrolytes and fluids which occurs with duodenal suction made this patient an exceedingly poor risk for a second operation. Miller-Abbott intubation was attempted on the eleventh hospital day, but a single isolated loop of ileum had formed which would not allow the balloon to pass into the small bowel. Adhesions were divided at a second operation, on the twelfth postoperative day, and an ileostomy performed. The patient died 24 hours later.

The one survival in the group (Case 55, P. H., No. 537,264) had a mechanical obstruction at the site of a residual appendiceal abscess. An ileostomy was performed and functioned well, apparently, because the vigorous peristalsis proximal to the point of obstruction caused a reflex of the fluid and gas which could be evacuated by the ileostomy.

COMMENT.—These patients are usually desperately ill, and one hesitates to subject them to the discomfort of fluoroscopic examinations, yet the passage of the tube without fluoroscopic guidance is time consuming and often impossible. All but one of our failures to pass the tube into the small bowel have occurred in this group. The results that follow early and successful intubation amply justify the procedure. Time consuming manipulation in the fluoroscopic room is not warranted, but the tip of the tube must be placed at the pylorus in order that it may progress spontaneously into the duodenum.

Our mortality figures for the two groups are not exactly comparable, since many of those in which the tube was passed successfully into the small bowel did not develop generalized peritonitis. As pointed out previously, however, five of our failures were in the first ten cases, in which we recommended surgery early, due to a lack of experience in the method.

Observations upon many cases will be required before the true value of intubation is established beyond a question, but the dramatic suddenness with which these patients were converted from a condition of alarming distention and serious outlook to one of comparative well-being by deflation, and food and fluids by mouth, is striking. The ileus accompanying a peritonitis adds a serious complication to a patient already struggling to survive an overwhelming infection. The relief by intubation of distention and its pressure effected on the circulation of the bowel plays an important rôle in helping the patient toward recovery.

Although the evidence is slight at present, it would appear that early de-

flation will prevent the formation of mechanical obstructions that occur when the bowel is left distended during the fibropurulent stage of the disease. Constrictions in the bowel lumen have been repeatedly demonstrated radiographically in these cases. Only two, however, have required operative relief. All fatal cases showed massive adhesions causing multiple points of obstruction. If mechanical obstruction does occur, the tube offers the best method for keeping the patient symptom free until infection with its soft adhesions subsides or until the adhesions can be liberated by a secondary operation. Moreover, with the tube acting as an ileostomy, the patient is maintained in an adequate nutritional state on a low residue diet and fluids by mouth.

GROUP 3: *Obstructions with Gangrene of the Bowel.*—The indiscriminate use of the Miller-Abbott tube in all cases of small intestinal obstructions would undoubtedly result in fatally delaying surgery in a certain number of cases with gangrene of the bowel. Care must be used in selecting the cases for intubation. Operation is advised in all cases of acute ileus with: (1) A history of a sudden onset of pain which persists between crampy attacks; (2) where localized tenderness is elicited or a tender mass is palpable; (3) where the white blood count remains increased, and temperature and pulse rate do not return to normal after adequate fluids have been administered; and, finally, (4) in a few cases where the diagnosis is so obscure that exploration is necessary for the proper evaluation of symptoms. Immediate operation was advised in nine cases, four of which did not have gangrene of the bowel and which would probably have been benefited by preoperative deflation. Fortunately, no case with gangrene of the bowel has had operation delayed for intubation purposes alone. It must be remembered that cases with gangrene are encountered in only about 5 to 10 per cent of the total cases of acute ileus, and surgery alone has yielded very poor results.

TABLE V

OBSTRUCTIONS WITH GANGRENE OF BOWEL

Case No.	Hospital No.	Age	Cause of Obstruction	Duration of Ileus	Summary of Miller-Abbott Treatment	Result
72	P. H., No 546,956	44	Volvulus of ileum, with perforation. Localized abscess. Local peritonitis	4 days	3 hrs. before operation. 18 days after operation	Recovered
73	P. H., No. 551,181	67	Strangulation of ileum, due to late postoperative adhesions	26 hrs.	After resection only. Controlled distention for 16 days, until second obstruction was corrected by second operation	Recovered
74	P. H., No. 531,770	14	Strangulation of ileum, due to late postoperative adhesions	16 hrs.	3 days after resection only	Recovered
75	P. H., No. 482,415	40	Strangulation of ileum, due to late postoperative adhesions	36 hrs.	Profound shock when first seen, 6 hrs. before resection and until death, 36 hrs. later	Died
76	P. H., No. 550,662	26	Strangulation of ileum, due to adhesions of pregnant uterus	60 hrs.	Profound shock when first seen, 5 hrs. before resection and until death 12 hrs. later	Died

CASE REPORTS—GROUP 3

Case 72.—P. H., No. 546,956: A male, age 44, was admitted with a five-day history of sudden onset of crampy abdominal pain, nausea and vomiting, diarrhea, and increasing distention. Operation was advised because of localized tenderness, elevated temperature, and increased white blood count. The Miller-Abbott tube was passed into the duodenum and continuous suction started while the patient was being prepared for operation. At operation, a volvulus of the ileum was found, with approximately six feet of gangrenous bowel which had perforated, producing a diffusing peritonitis around a localized abscess. Resection with end-to-end anastomosis was accomplished, and the wound drained with two large rubber tubes and a silk tampon. The Miller-Abbott tube was allowed to progress postoperatively, and fluids were given by mouth after the second postoperative day. Suction was discontinued on the eighth postoperative day, which was followed by a prompt recurrence of the ileus, which was again controlled by starting continuous suction. The tube was removed on the eighteenth postoperative day, when no ileus had occurred after a second two-day trial without suction. The recovery thereafter was uneventful.

Case 73.—P. H., No. 551,181: A female, age 67, was admitted with a 26-hour history of sudden onset of crampy abdominal pain, increasing distention, nausea and vomiting. The temperature was elevated and the white blood count was increased. The patient had had a hysterectomy 20 years previously.

Immediate operation was performed, at which adhesions were divided, and the resection of a 20 cm. loop of gangrenous ileum, which was found in the pouch of Douglas, undertaken. A Murphy button was used to effect the anastomosis. The Miller-Abbott intubation was started immediately after operation, and the patient was kept deflated and comfortable for four days, when trial without suction resulted in a recurrence of the ileus. Roentgenologic studies demonstrated a second obstruction, caused by the Murphy button's having been caught in a sharp angulation distal to the anastomosis. The patient remained comfortable, with suction continued, until the Murphy button could be removed on the sixteenth postoperative day. Recovery was slow but uneventful.

Case 74.—P. H., No. 531,770: A female, age 13, three months after an appendicectomy, was admitted with a history of sudden onset of crampy abdominal pain, and nausea and vomiting beginning 16 hours previously. The temperature was normal but the white blood count was increased. No distention could be noted in the abdominal roentgenograms, but a tender mass was palpable in the right lower quadrant. Operation was undertaken, at which a 12 cm. loop of gangrenous ileum was removed, and an end-to-end anastomosis accomplished. The Miller-Abbott tube was passed immediately after operation. The abdomen remained soft during three days of small intestinal suction, at which time the patient passed a normal stool. The tube was removed and recovery was uneventful.

Case 75.—P. H., No. 482,415: A female, age 40, was admitted with colicky epigastric pain, nausea and vomiting, without distention, for 24 hours' duration. Appendicectomy had been performed for acute mesenteric lymphadenitis two months previously. The roentgenograms of the abdomen showed no evidence of ileus. Due to an increased white blood count, localized tenderness, and a questionable mass in the right lower quadrant—all present on the previous admission—the patient was admitted with a diagnosis of a recurrence of acute mesenteric lymphadenitis. Distention developed rapidly 24 hours later, and the patient went into profound shock. The Miller-Abbott tube was introduced into the stomach and gastric suction started while the patient was being prepared for operation. At exploration, a long loop of ileum was found strangulated by postoperative adhesions, which made a resection necessary. The patient became pulseless on the table. She responded to additional transfusions, but died in shock, 12 hours later. No attempts had been made to advance the Miller-Abbott tube beyond the stomach.

Case 76.—P. H., No. 550,662: A female, age 26, was admitted to the Obstetric Service, with a history of sudden onset of crampy abdominal pain, nausea and vomiting, and increasing distention in the seventh month of her pregnancy. Two days later she

was delivered of a premature fetus, but her symptoms continued. When seen by the surgical consultant, two days after delivery, the patient was in shock, markedly distended, and had acute, generalized abdominal tenderness. The Miller-Abbott tube was passed into the duodenum and suction started while the patient was being prepared for exploration. At operation, old adhesions between the uterus and appendices epiploica of sigmoid were found encircling and strangulating about one-third of the small bowel, which required a massive resection. The patient died in shock six hours after operation.

COMMENT.—The Miller-Abbott tube has a place in these cases in the usual stormy postoperative period. The first two cases were greatly benefited and the third made more comfortable during the immediate postoperative period.

FIG. 11.—Carcinoma of Splenic Flexure of Colon with Large Bowel Distention. Plain roentgenogram of abdomen showing persistent large bowel distention after 48 hours of continuous suction, with the Miller-Abbott tube in the terminal ileum.

The remaining two cases were in profound shock when intubation was requested, too late for either surgery or intubation.

Large Bowel Obstruction.—In mechanical, large bowel obstruction with acute distention, our experience seems to indicate that cecostomy remains the treatment of choice. In five such cases, the Miller-Abbott tube was passed to the ileocecal valve, without relieving the large bowel distention (Fig. 11), although decompression of the small bowel did relieve nausea and vomiting. However, the time required for the tube to reach the ileocecal region may well

allow a spontaneous rupture of a distended cecum and there is, therefore, some danger in delaying operation. Decompression of the large bowel probably fails because the ileocecal valve, for some reason, seems to act as a barrier to the passage of the tube when cecum is distended.

Notwithstanding the foregoing, patients requiring large bowel resections, but who show no distention prior to operation, can be saved a preliminary cecostomy by passing the tube before operation. Continuous suction can be maintained after resection and fluid and food given by mouth, after the second postoperative day, without causing distention or discomfort. The tube can be kept in the ileum until the colostomy or the bowel anastomosis functions normally. Six such cases have been treated with gratifying results. These cases will be reported in detail in another communication.

TABLE VI

SUMMARY OF CASES OF SMALL INTESTINAL OBSTRUCTION TREATED WITH THE MILLER-ABBOTT TUBE AND SURGERY

Type of Obstruction	No. of Cases	Operations for Ileus	Died	Mortality
Noninflammatory Obstructions	50*	27	1	2.0%
A. Paralytic type	12	1	0	0
B. Mechanical type	38	26	1	2.7%
Obstructions with Peritonitis	21	10	7	33.3%
Tube passed into small bowel	14	2	1	7.1%
Tube *failed* to pass into small bowel	7	8†	6	85.7%
Obstructions with Gangrene of Bowel	5	6†	2	40.0%
Total cases	76	43	10	13.2%
Total cases with tube passing into small bowel	68	35	4	5.9%

* One case discontinued. Patient hysterical.

† Two cases required two operations for ileus.

Discussion.—One of the most important requirements of the surgeon and radiologist in introducing the use of the Miller-Abbott tube is *patience*. It was difficult to secure cooperation of the surgeon in earlier cases because, heretofore, all cases with intestinal obstructions have been treated as a surgical emergency and the surgeon hesitated to accept a method, still in the experimental stage, which often required a delay in operation as long as 24 to 48 hours. Apparently, many surgeons have tried to use the method and discarded it as impractical after failing to reach the duodenum within a few hours. Both Abbott and Johnston mention this difficulty in cases with distention, and point out that considerable time and careful attention are necessary for successful intubation. One surgeon recently stated that he had tried to pass the tube for 45 minutes but, of course, failed and has since discarded its use. Several of our own early failures were due to the fact that sufficient time was not allowed for the preliminary deflation of the stomach, but now, with growing confidence in the method, we do not hesitate to delay operation two days, if

necessary, to pass the tube into the duodenum. During this period, gastric suction alone will maintain the patient in as good or better condition if the fluids aspirated from the stomach are replaced in adequate amounts by parenteral routes.

SUMMARY

(1) Seventy-six cases of small intestinal obstruction have been treated with the Miller-Abbott principle, as originally reported by Abbott and Johnston. The procedure has been used: (1) In paralytic ileus to deflate the bowel and demonstrate the patency of the bowel lumen; (2) in mechanical obstructions for deflation, diagnosis and localization of the lesion; (3) for the preoperative administration of food and fluids by mouth, while the tube is serving the purposes of an ileostomy; and (4) for the control of postoperative distention in any type of case.

(2) A simple method of intubation is outlined which has been successful in passing the tube into the small bowel in 68 of the 76 cases. It is significant that five of the failures occurred in the first ten cases treated.

(3) Each case of small intestinal obstruction presents an individual problem in intubation, but the essential features used in the selection of cases are presented by dividing them into three clinical groups which require, for the most part, a similar method of procedure.

(4) The diagnostic value of the Miller-Abbott tube is graphically illustrated in the detailed reports of typical cases in each group.

(5) The therapeutic value of the Miller-Abbott tube is emphasized by the low mortality figure of 5.9 per cent in 68 cases in which the tube was successfully employed. Previous mortality figures from this hospital, reported by Van Beuren and Smith,[9] range from 66.6 per cent (during 1916–1919) to 27.6 per cent (during 1932–1935).

(6) Cecostomy is the treatment of choice in cases with large bowel obstructions showing distention prior to operation, but unnecessary cecostomies may be avoided in cases requiring large bowel resections where there is no distention prior to operation.

(7) Gangrene should be suspected and an immediate operation recommended for all patients giving a history of a sudden onset of pain which persists between crampy attacks and who show localized tenderness over a palpable mass.

CONCLUSION

The Miller-Abbott method of small intestinal intubation is an *indispensable* aid to the proper management of small intestinal obstructions.

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ACUTE APPENDICITIS

A TWENTY-YEAR CLINICAL SURVEY

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ACUTE APPENDICITIS still remains a mocking challenge to those who practice the art and science of medicine, in spite of all the advances made by surgery during the past two decades.

More than 20 years ago, Murphy decried the apparent increase in the death rate of appendicitis when he forcefully stated: "In looking up recently the hospital statistics on the results of operations for appendicitis, what mortality rate do you suppose I found? . . . The average hospital mortality rate is just a little over 10 per cent! There is no excuse for a mortality rate of 10 per cent in appendicitis. The rate is simply shocking. These patients did not die because of the operation—do not misunderstand me—they died in spite of it. Procrastination was the cause of death—the almost criminal cause." And now, more than two decades after these memorable words were uttered—what do we find? An average mortality rate throughout the United States of over 10 per cent.

Acute appendicitis continues to be the most frequent indication for major surgical intervention to-day. Yet it ranks second only to cancer among surgical diseases as a cause of death for all ages. According to Ochsner, in 1936, one person in the United States died every 29 minutes from appendicitis.

Vital statistics of the United States, for the year 1920, place the mortality rate for acute appendicitis at nine for each 100,000 of population, and at 14.3 per 100,000 for the year 1934; 18,129 deaths! The Metropolitan Life Insurance statistics indicate that the mortality rate of acute appendicitis rose from 10.6 per 100,000 for the period 1911 to 1914 inclusive, to 14.1 for the period from 1927 to 1930, inclusive. In New York City, the death rate from appendicitis averages about 14 per 100,000 of population yearly; 1,149 deaths occurring in New York City in 1934 were due to appendicitis.

Of 4,542 cases of acute appendicitis for the years 1921 and 1931, studied by Krech, in 14 Grade A hospitals, the operative mortality was 7 per cent. In these 14 excellent institutions, no appreciable decrease in the mortality rate from acute appendicitis had occurred in a decade—an appalling situation, an indictment against the medical profession!

While a review of the experience of the outstanding clinics shows figures

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better than a mortality rate of 7 per cent, in many cases, the toll is nevertheless too high. Thus, Seifert reports a total mortality for the decade, 1911 to 1920, to be 6.8 per cent at the Wurzberg University clinic and 3.5 per cent during the next decade (1922–1931) in 2,763 cases. Reviewing 2,000 cases of acute appendicitis, Swain reported an average mortality rate of 3.25 per cent, in 1934. Wevill and Wallace studied 8,265 cases at the Royal Infirmary at Edinburgh, and found that a mortality rate of 4.4 per cent had not significantly diminished over a 10-year period. Z. Muller performed 1,087 appendicectomies over an 11-year period, and reported a mortality rate of 6 per cent for the acute type. Donaldson analyzed 2,700 cases of acute appendicitis at the Mercy Hospital in Pittsburgh, and found a death rate of 4.81 per cent. McKenna reports on 1,257 acute cases at St. Joseph's Hospital during the years 1922 to 1935, with fatalities reaching 5 per cent. In 1,734 cases studied at the Anderson County Hospital, Young found a total death rate of 4.3 per cent. In 1934, Stanton analyzed 16,424 cases with a death rate of 5.4 per cent, and found that 20 years prior, in 4,343 cases, the toll was 6.2 per cent. Jensenius analyzed 1,933 cases admitted to the Bespebjoerg Hospital, Copenhagen, during 10 years. Of the 1,592 patients operated upon, 109 died, or 6.85 per cent. Rhodes made a clinical review of 1,000 consecutive cases of acute appendicitis at the San Francisco Hospital, and during the 10-year period, found an operative mortality of 3.6 per cent. Lazzarini recorded his observations on 800 cases of acute appendicitis operated upon in the Ospedale Maggiore of Milan, with a mortality rate of 12 per cent. In a survey of 10,000 cases treated at the Providence Hospital of Detroit, Davis reported a mortality rate of 3.8 per cent. A notable contribution is that by Guerry,[14] who by delayed operation in 139 cases, was able to reduce the mortality rate from 10 per cent in diffuse peritonitis to 1.5 per cent. Reid, in a study of 2,806 cases, during the past 12 years, was able to reduce the rate from 9.5 to 5.4 per cent. Holden and Wells analyzed 3,526 acute cases in four hospitals in San Diego, with a death rate of 8.2 per cent. Reviewing 518 cases of the acute type in the University of Minnesota Hospitals, Sperling and Myrick found no appreciable decline in mortality had occurred during 20 years. Ray, more recently, reported a mortality rate of 2.1 per cent, in 886 cases of acute appendicitis operated upon at the New York Hospital.

Scope of Investigation.—Confronted with this array of figures from various clinics, and fully aware of the dissatisfaction of the profession with the results obtained, we were interested in studying the problem at our own institution. Our interest was two-fold. In an institution where the acute surgical service is very active and where operations for acute appendicitis over a period of 20 years totaled almost 9,000 cases, we were quite certain that instructive information would result from a detailed study; something constructive, to aid in dismissing the indictment of too high a mortality. In addition, we were interested to find out how we fared in comparison with other clinics—whether we were justified in continuing our time-tried methods, or whether we should discard them.

This report represents every case of acute appendicitis operated upon at the Jewish Hospital of Brooklyn during the period of 20 years (January 1, 1915–December 31, 1934, inclusive). No case is included unless proven by pathologic examination to be one of acute appendicitis. Wherever some doubt existed as to the acuteness of the process, such case was omitted. However, in those cases where no appendicectomy was performed, the operative findings were such as to leave no doubt as to the cause of the peritoneal involvement.

TABLE I

REVIEW OF MORTALITY RATES AS REPORTED IN LITERATURE

	Period	Cases	Deaths	Rate
Krech[1]	1921 and 1931	4,662	318	7.0%
Seifert[2]	1911–1920	1,350	92	6.8
	1922–1931	1,413	49	3.5
Swain[3]		2,000	65	3.25
Wevill and Wallace[4]		8,265	364	4.4
Muller[5]		1,087	65	6.0
McKenna[7]		1,257	63	5.0
Young[8]		1,734	75	4.3
Stanton[9]	1934	16,424	887	5.4
	1914	4,343	270	6.2
Jensenius[10]		1,592	109	6.85
Rhodes[11]		1,000	36	3.6
Lazzarini[12]		800	96	12.0
Davis[13]		10,000	380	3.8
Reid[15]		2,806	180	6.4
Holden and Wells[16]		3,526	290	8.2
Sperling and Myrick[17]		518	29	5.6
Ray[18]		886	19	2.14
Morse and Rader (present report)	1915–1934	8,727	188	2.15
Totals		73,070	3,575	4.89%

In this 20-year period under consideration, 8,727 cases were examined in considerable detail. In order to standardize our statistical findings, we have employed certain terms, and to be sure of our terminology, a few definitions are essential.

In reviewing the literature, appendicitis, as presented in the acute form, may be either nonperforated or perforated. Nonperforated acute appendicitis our pathologist has classified as acute catarrhal, acute suppurative or acute gangrenous. Perforated instances of acute appendicitis we have subdivided into those where: First, the perforation resulted in no local or diffuse peritonitis, but merely caused either the omentum, or some viscus to attach itself to the perforation and no peritoneal pathologic process was encountered macroscopically. Second, those perforated lesions which precipitated active peritoneal complications, such as local peritonitis, diffuse peritonitis. Third, definite abscess formation. In our presentation, we have purposely omitted the term "general" peritonitis, and considered all forms of spreading peritoneal

inflammation diffuse, because of the possible error that any such term as general peritonitis may carry with it.

Proper evaluation of statistics in acute appendiceal inflammation must carry with it the exact type of the acute process found, for the prognosis in the nonperforated variety certainly is much better than in the perforated form.

The question may arise, of what value are statistical reports? We believe much can be learned, not in praising the general outcome, but in trying to analyze the cause of our failures, as we believe that the last word in the treatment of acute appendicitis has not yet been said. To be sure, operation as soon as the diagnosis is made is still an excellent treatment; but how shall we improve our results in the late, complicated, neglected cases? Can that mortality rate be reduced?

TABLE II

ANNUAL MORTALITY RATE, JEWISH HOSPITAL SERIES

Period 1915–1934, inclusive

Year	Cases	Deaths	Mortality Percentage	
1915.....	397	12	3.02	
1916.....	442	19	4.29	
1917.....	404	13	3.21	
1918.....	405	9	2.22	
1919.....	417	12	2.87	Average
1920.....	394	9	2.28	2.73%
1921.....	393	13	3.30	
1922.....	400	9	2.25	
1923.....	448	11	2.45	
1924.....	433	6	1.37	
1925.....	398	4	1.00	
1926.....	405	5	1.23	
1927.....	469	13	2.77	
1928.....	346	6	1.73	
1929.....	413	9	2.99	Average
1930.....	468	14	2.17	1.63%
1931.....	556	0	0.00	
1932.....	471	2	0.42	
1933.....	563	11	1.95	
1934.....	505	11	2.17	
Totals....	8,727	188	2.15	

Acute appendicitis is not a finished subject. Of course, early operation would eliminate all our problems. Early operation carries with it the necessity of early diagnosis. Early diagnosis does not always carry with it the consent of the patient to submit to operation. Early diagnosis is not always a simple problem, and although acute appendicitis may be one of the most apparent diagnoses, yet there is not one of us who has not been chagrined to learn that we erred. It may be so protean in its manifestations, that the acuity of any surgeon or internist alike may be taxed to the limit. How to improve our

diagnostic acumen may require nothing other than the realization of how varied may be the clinical picture that presents itself. We hope, in the present review, to recognize every variety of appendicitis that has been encountered. As stated previously, the early variety requires very little to be desired, for we can, as have many others, boast of a mortality rate of less than one-third of 1 per cent, *i.e.*, one death in 300 cases. However, the story is far from encouraging in the late or perforated type, for here the deaths mount in our diffuse peritonitis group to one in three. It is this group that commands our particular consideration, and it is to this group that we shall chiefly concentrate our analyses.

We have, for completeness, analyzed our 20-year study in yearly considerations, *i.e.*, examined the improvement or lack of improvement during the period reviewed.

Sex incidence, to us, seemed a rather unimpressive factor; however, a detailed study was made.

Age—a rather important consideration, especially at the extremes of life—has been a factor that deserved complete investigation—in fact, so much so that we believe it warrants particular study. This analysis will be considered in detail in another communication.

The time element, too, is extremely important, not only in mortality outcome, but in morbidity results; and we have scrutinized, as carefully as possible, the results of those operated upon after a varying number of days of delay.

Temperature, pulse and laboratory data, too, have been extensively analyzed, as the reports attached will show.

There can be no doubt that the greatest single factor that determines the prognosis in acute appendicitis is early operation. All statistical reports bring home the fact, and anyone with surgical experience cannot but be convinced of this axiomatic conclusion. Yet the fact still remains that delay is rampant and the neglected case must be managed.

Our records are creditable, and we are gratified to report progress in the results, during the second decade under consideration, as compared with those of the first 10-year period.

Mortality Rate.—Thus, we were able to reduce our mortality rate, for the decade 1925–1934, to 1.63 per cent, from 2.73 per cent, for the period 1915–1924. The number of cases of our total series was 8,727; 4,133 operated upon during the first decade of our series, and 4,594 during the second half of our 20-year period. There can be no doubt that statistics, in themselves, have little value, for the better results may merely represent good fortune in operating upon mildly afflicted cases. However, when we consider that over a period of 20 years, nearly 9,000 cases were encountered, surely some instructive conclusions should be developed.

In reviewing Table II, we were encouraged to find that during the year 1931, 556 cases were operated upon without a single death; and the following

year, 471 cases showed but two deaths; or two deaths in 1,027 cases; a truly remarkable record.

Sex Incidence.—We are of the opinion that sex has very little, or no significance in relation to the problem of acute appendicitis. However, in this statistical study, for the purpose of thoroughness, there are a few observations which we have noted. In common with the experience of others, we have found a slight preponderance of males over females (4,833 to 3,894), a ratio of approximately 5 to 4. There were 116 deaths among the males, a mortality percentage of 2.4. The female deaths numbered 72, a rate of 1.84 per cent.

Age Incidence and Mortality.—Of more significance is the study of the relationship of age incidence to mortality. Here, too, our findings are in accord with those of other investigators. The frequently repeated statement that the mortality rate of acute appendicitis is greatest at the extremes of life is well corroborated by our statistics. Table III clearly illustrates this. Thus, in the first decade of life, there were 1,610 cases operated upon, with 44 fatalities, a death rate of 2.73 per cent. This is three times as high as the rate in the next succeeding decade, where our largest group of cases, according to age, occurred. Of course, a death rate of 2.73 per cent may not seem unduly high. However, in a subsequent report, where we intend to study this problem more thoroughly in children below the age of five, we know definitely that the toll is higher. Briefly, this is due to the difficulties of establishing an early diagnosis in the very young, as well as the more rapid progression of the pathologic process; the vulnerability of the peritoneum to infection; and the lack of omental protection. Acute appendicitis is essentially an illness of adolescence and early adult life. Between the ages of 11 and 40, there were a total of 6,128 in our series of 8,727, about 70 per cent of all studied.

TABLE III

AGE INCIDENCE IN RELATION TO MORTALITY RATE

Age	Cases	Deaths	Mortality Rate
To 11	1,610	44	2.73%
11–20	2,822	24	0.85
21–30	2,182	23	1.05
31–40	1,134	28	2.47
41–50	564	37	6.56
51–60	266	13	4.88
61–70	114	19	16.16

It is interesting to note that the death rate was lowest during the second decade, slightly higher in the third decade, definitely mounting in the fourth and then jumping rather rapidly to a figure of 6.5 per cent in the fifth decade. Between the ages of 51 to 60, the rise was not appreciable. However, beyond age 60, the figure assumes formidable proportions. Here the toll is at its greatest, 16.16 per cent. The difficulty does not lie in making the diagnosis. Age brings with it the complications of degenerative processes, and metabolic disorders, so that the human organism is less able to cope with acute infectious

processes. Thus, in reviewing our mortalities, we shall find later that a goodly number of our aged individuals succumbed because of impaired cardiovascular systems, and metabolic diseases, as well as from peritonitis.

Duration of Illness and Mortality.—Undoubtedly, the most important single factor in lowering the mortality of acute appendicitis is the rapidity with which surgical intervention is undertaken. McBurney, Murphy, Deaver and many others have emphasized and reiterated this fact. As long as the infectious process remains localized to the appendix, the mortality rate will be kept at an irreducible minimum. Once the pathologic process extends beyond the confines of the organ to involve the peritoneum, complications, with an attendant rise in morbidity and mortality, ensue. To prevent this, it is necessary to operate as early as possible. As a rule, during the first 24 hours, the inflammation remains localized to the appendix. While we encountered several cases where perforation had occurred within the 12-hour period after the onset of symptoms, their paucity was such as to strikingly emphasize the generalization just made.

TABLE IV

MORTALITY IN RELATION TO DURATION OF ILLNESS

Days Ill Before Operation	Cases	Deaths	Mortality Rate
First 24 hrs.	2,850	17	0.59%
1–2 days	2,424	35	1.44
2–3 days	1,435	32	2.23
3–4 days	742	33	4.44
4–5 days	384	25	6.51
5–6 days	190	10	5.26
Over 6 days	645	33	5.11
Unknown	57	3	5.26
Comparative mortality, first 3 days			
First 24 hrs.	2,850	17	0.59
First 48 hrs.	5,274	52	0.98
First 72 hrs.	6,709	84	1.24

In our series, 2,850 cases were operated upon within 24 hours after the onset of symptoms. These represented, roughly, about one-third of our series. Seventeen in this early group died, a mortality rate of 0.59 per cent. In other words, the average chance of recovering from acute appendicitis, when subjected to surgery within 24 hours of the onset, was 198.8 out of 200 cases, which probably represents an irreducible minimum. In the second 24 hours of illness, 2,424 cases were operated upon; 35 succumbed and the mortality rate rose to 1.44 per cent—almost three times as high as during the first 24 hours. With each succeeding day of delay, the appended Table IV graphically depicts a rise in the death rate. Five thousand, two hundred seventy-four cases were operated upon within 48 hours, with a creditable recovery record of 99.02 per cent. Of patients operated upon during the third day of illness, we had 1,435, with 32 failing to survive, showing a mortality rate

almost four times as high as that encountered in the first group of cases. Thus, over three-quarters of our cases were subjected to operation within 72 hours of onset, with a mortality rate of 1.24 per cent. After the third day, the death rate climbed rapidly to 4.4 per cent between the seventy-second and ninety-sixth hours, and to 6.5 per cent from the fourth to fifth days. Fortunately, less than one-quarter of our cases came to operation after the third day; and this fact unquestionably contributed to our low death rate. After the fifth day of illness, operation yielded recoveries in somewhat less than 95 per cent of the cases.

There are some who advocate the postponement of operation after acute appendicitis has existed for over 72 hours. While there may be some merit in this practice, such has not been our procedure. As soon as the diagnosis was made and the patient hospitalized, surgical intervention was instituted. Each case has to be evaluated individually, and not treated by any rule of thumb. Many of our cases operated upon after the third day still showed a lesion confined close to, if not solely to, the appendix. There were, it is true, a number of patients in a moribund state, who were subjected to surgery. This constituted poor judgment and increased our mortality rate. On the whole, however, we believe excellent judgment was displayed as to the proper time to operate. In closing the discussion of this particular aspect of the problem, let us reemphasize: Operate within 24 hours of the onset of symptoms, and, other things being equal, the deaths in acute appendicitis will be reduced to the lowest figure humanly possible.

Temperature Reaction.—A rather detailed study was made of the temperature reaction to acute appendiceal inflammation. Referring to Table V, we observe that the majority of cases did not have an elevation of temperature above 102° F. As a matter of fact, 6,790 cases, or over 75 per cent of our total, showed a febrile reaction below 102° F. In less than 25 per cent of the cases was there a temperature range from 102° to 105° F.

TABLE V

TEMPERATURE REACTIONS

Degrees Fahr.	No. of Cases	Percentage of Total
Under 100.....	1,831	20.97
100–101.....	2,794	32.11
101–102.....	2,165	24.80
102–103.....	1,203	13.78
103–104.....	534	6.11
104–105.....	158	1.81
Over 105.....	38	0.41
Unknown.....	4	0.01

The majority of the cases showing a low febrile movement fell into the group of uncomplicated cases, *i.e.*, without peritoneal reaction or involvement. Those cases with fever above 102° F., generally speaking, were complicated by some degree of peritonitis.

Our impressions from the study of this aspect of the disease is that acute appendicitis *per se* is attended with only a moderate febrile reaction; and the presence or absence of fever is of limited aid in the differential diagnosis. We have observed many cases of acute gangrenous inflammation of the appendix with temperatures ranging below 100° F. So that, in the presence of other signs pointing to a diagnosis of acute appendicitis, a normal or slightly elevated temperature should not be permitted to sway one away from the opinion entertained.

TABLE VI

RELATION OF TEMPERATURE TO DURATION OF ILLNESS

Temperature	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	Over 7 Days
Under 100	842	417	218	103	62	22	153
100–101	1,431	568	298	146	77	42	169
101–102	1,042	564	263	103	60	31	115
102–103	471	375	162	77	31	17	70
103–104	178	160	86	32	17	9	45
104–105	40	55	25	8	11	7	11
Over 105	12	13	2	5	2	2	2

Table VI shows the variations of the temperature reactions according to the duration of the illness. This, too, seems to corroborate the fact that during the first 48 hours, when the greatest number of uncomplicated cases were seen, there also occurred the greatest number of cases with low febrile reaction.

Pulse Rate.—Brief mention may be made relative to the pulse rate in acute appendicitis (Table VII). The pulse rate on admission was noted in our analysis in every case (except in a few infants, where the pulse rate was not recorded).

We may infer that in a good majority of cases, acute appendicitis is accompanied by a definite elevation in the pulse rate (70 per cent), occurring somewhere between 91 and 120 plus.

TABLE VII

ANALYSIS OF PULSE RATE

Pulse	No. of Cases	Percentage of Total
Under 70	110	1.25
70– 80	755	8.64
81– 90	1,579	18.08
91–100	2,289	26.22
101–110	1,289	14.76
111–120	1,633	18.70
Over 120	1,052	12.35

Blood Reaction.—The response of the leukocytes to acute inflammation of the appendix was studied in searching detail. We attempted to establish the relationship, if any, between leukocytic reaction and the elevation in temperature. Our investigation served to show no correlation in this respect. Pro-

portionately, there were just as many instances with high leukocyte counts where the temperature range was 100° F. or below, as there were when the febrile response was 103° F. and over. The extremes of blood counts varied from 8,000 W.B.C., with 70 per cent polymorphonuclear leukocytes, to 39,000 W.B.C., with 95 per cent polymorphonuclear leukocytes. In general, our studies showed that acute appendicitis was attended with a leukocytosis averaging between 12,000 and 18,000, and a polymorphonuclear count between 75 and 90 per cent.

Incidence of Previous Attacks.—A study was made of those cases of acute appendicitis that had had previous acute attacks. Referring to Table VIII, one notes some interesting data.

TABLE VIII

ANALYSIS OF INCIDENCE OF PREVIOUS ATTACKS

No. of Cases	Pathologic Process	First Day	Second Day	Third Day	Fourth Day	Fifth Day	Sixth Day	Seventh Day
805	Acute catarrhal	318	204	98	46	34	17	88
862	Acute suppurative	476	189	79	46	22	7	43
556	Acute gangrenous	395	159	50	18	6	1	17
335	Acute perforative	144	115	50	8	3	6	9
127	Abscess	19	25	29	10	8	3	33
2,685	Totals	1,262	692	306	128	73	34	190

In all, there were 2,685 cases operated upon that had had one or more previous attacks, about 30 per cent of the total. Of these, we find that in the first decade studied, 1,465 cases out of a total of 4,132, or 35 per cent, had had previous attacks. In the second decade, out of a total of 4,595 cases coming to operation, only 1,220 cases, or 26 per cent, had been previously ill with appendicitis. Thus, in one decade, there was a reduction by 25 per cent of patients who had had previous attacks. We believe this to be quite significant. To us, it indicates that both physicians and patients have become more "appendicitis conscious" and are less willing to temporize with this condition. To further substantiate this contention, we find that 1,262, or roughly 50 per cent, of patients who had had previous attacks were operated upon during the first 24 hours of the present illness. This percentage excels by far the figure of 32 per cent previously reported, of the 2,850 cases in our total series, that came to operation during the first 24 hours of illness.

In reviewing the statistics in Table VIII, we feel that the occurrence of previous attacks does not seem to appreciably influence the relationship existing between the pathology encountered and the duration of the present attack.

Anesthesia.—Until 1927, inhalation anesthesia, ether alone, nitrous oxide and ether, or nitrous oxide augmented by local novocain infiltration, was employed almost exclusively. A very small number of operations were performed under local anesthesia alone. In 1927, spinal anesthesia was introduced into our institution, and 36 appendicectomies were performed for acute

appendicitis under this anesthetic. From then on, all have favored the use of spinal over inhalation anesthesia. Not only have we obtained better relaxation, but we have definitely secured a lowering of postoperative complications due to the anesthetic *per se*. Another point of importance is, that with spinal anesthesia, we have been able to avoid the "pumping action" of the abdomen incident to induction with a general anesthetic and its harmful effect on peritoneal inflammation.

Six thousand, six hundred forty-one cases were operated upon under general inhalation anesthesia, with 90 instances of postoperative respiratory complications, an incidence of 1.35 per cent. Of 1,990 appendicectomies, performed under spinal anesthesia, only two patients developed respiratory morbidities (0.1 per cent). In 96 cases, local anesthesia was employed, and in one patient a postoperative respiratory complication arose. Thus in our series, spinal anesthesia proved to be the most favorable.

Pathology and Mortality.—Again, let us reiterate that gross statistical figures carry no weight and teach nothing. Analyzing these mortality rates, in terms of pathologic entities, during the 20-year period under consideration, shows that 1,754 cases were diagnosed, pathologically, as acute catarrhal appendicitis. Four of these patients died, a rate of 0.22 per cent; 2,771 were of the acute suppurative type—of these eight died, a mortality rate of 0.28 per cent. During that same period, 1,939 cases of acute gangrenous appendicitis were encountered, with 20 deaths—a rate of 1.03 per cent. In other words, appendicectomy was performed in 6,464 cases of nonperforated appendicitis with but 32 deaths, or 0.50 per cent; or less than one death in 200 cases, and that where 4,270 cases were acutely suppurative or acute gangrenous (Table IX). If such a record resulted in our perforated variety of appendicitis, then, and only then, could we rest as having solved our problem of acute appendicitis with dispatch. Unfortunately, this is not the case.

TABLE IX

MORTALITY RATE IN CASES OF NONPERFORATED APPENDICITIS

Type of Pathology	Procedure	No. of Cases	Deaths	Mortality Rate	
Acute catarrhal	Stump inversion	1,753	4	0.22%	0.22%
Acute catarrhal	Without stump inversion	1	0	0.00	
Acute suppurative	Stump inversion	2,754	8	0.28	0.28%
Acute suppurative	Without stump inversion	17	0	0.00	
Acute gangrenous	Stump inversion	1,906	18	0.94	1.05%
Acute gangrenous	Without stump inversion	33	2	6.06	

In explanation of Table IX: It has been our practice to invert appendicular stumps in performing appendicectomy, and where such had not been carried out, there must have been entailed, such pathologic involvement of the cecum as to forbid stump inversion. However, since no peritoneal involvement of the acute process presented itself, the cases must still be considered, and rightly so, as nonperforated.

TABLE X

MORTALITY RATE IN CASES OF PERFORATED APPENDICITIS

Type of Pathology	Procedure	No. of Cases	Deaths	Mortality Rate	
Perforated appendicitis	With stump inversion	964	15	1.55%	1.56%
	Without stump inversion	60	1	1.66	
Abscess	With stump inversion	419	24	5.72	6.02%
	Without stump inversion	100	10	10.00	
	Without appendicectomy	144	6	4.17	
Local peritonitis	With stump inversion	303	16	5.28	6.54%
	Without stump inversion	30	6	20.00	
	Without appendicectomy	3	0	0.00	
Diffuse peritonitis	With stump inversion	172	41	23.80	32.50%
	Without stump inversion	41	17	41.50	
	Without appendicectomy	27	20	74.00	

The results of our perforated cases (Table X), leave much to be desired, in spite of the fact that they compare favorably with many, if not all, of the better clinics. Those perforated cases, that presented little or no macroscopic peritoneal involvement, were 1,024 in number, with 16 deaths, a rate of 1.56 per cent. Even this record could be well tolerated, but, when we begin to examine our results with local peritonitis, abscess formation and diffuse peritonitis, there can be no doubt but that there is room for improvement. As could be well expected, the results with local peritoneal involvement and those with abscess formation present practically identical figures; namely, 663 cases of acute appendicitis with resultant perforation and abscess formation yielded 40 deaths, a 6.03 per cent mortality rate; whereas 336 perforated appendices with local peritoneal inflammation resulted in 22 deaths, or 6.54 per cent. Therefore, it can be understood why both these entities should be considered under one category. If this group is so considered, 999 cases were encountered with 62 deaths, a rate of 6.2 per cent. The deaths in this group should be instructive; and in our analysis of those who succumbed, we hope much may be elucidated.

Perforated appendicitis with diffuse peritonitis is a blot that must be eradicated. So long as the medical profession allows the appendiceal perforation to spread its infective material throughout the peritoneal cavity, just so long will the death rate of appendicitis remain where it is. There can be no excuse for a diffuse peritonitis in acute appendicitis. Perforations may occur, but certainly there can be no justification for allowing the peritoneum to be virtually inundated with the infection. Perforations may occur early, probably too soon for the physician to help, but, certainly, proper care can prevent transforming a local peritonitis into a diffuse one.

Patients must be taught the danger of using cathartics to relieve abdominal pain. Physicians, too, must be impressed with the realization that there can be no condonation for effecting a bowel evacuation that results in diffuse peritonitis. There can be no midway course, when the diagnosis of

acute appendicitis is even suspected. Either we treat the patient as a potential peritonitis case or operate at once. There can be no defense for any *modus operandi* that stimulates peristalsis. One might as well knead the intestinal tract with the offending organisms, and see to it that no serosal surface remains uncontaminated. No patient, suspected of acute appendicitis, should be allowed to remain at home. If observation must be resorted to, the hospital offers better facilities for such observations.

These patients, when catastrophic results ensue, are certainly more advantageously treated, if not subjected to transportation in the presence of local peritonitis. Fluids are more easily administered parenterally in an institution where such procedures are routinely performed. Expert observation certainly transcends familial hysterical kindness. To us, there can be no doubt that these patients belong in hospitals, and the sooner we can educate our clientele to that fact, the sooner may we obtain better results. There can be no doubt that if we must err, let us err on the side of hospitalizing too often, rather than too late.

Of our 240 cases with diffuse peritonitis, 77 died, one case in three. Almost unbelievable!—and this 50 years after Reginald Fitz wrote on perforating inflammation of the vermiform appendix. None of these cases was in the hospital to be observed. All were operated upon soon after admission. The value of such therapy will be discussed later, but one incriminating feature is the fact that these patients, at this day and age, had allowed themselves or had been allowed, by those who should have known better, to reach such a state of peritoneal infection.

Should this communication bring home but this one point, it shall not have been in vain. Let the family know that you suspect appendicitis. Let them realize late transportation is dangerous. Let us teach the doctrine of early hospitalization in suspected cases of appendicitis. Let us treat suspected cases as they should be treated. Let us come to the realization that no one can predict the ultimate outcome of any acute appendicitis suspect. Let us rather err in too early operation than in one too late.

Operative Technic.—Much has been written favoring each incision employed in operations for acute appendicitis. Before stating our views on this important problem, may we say that each surgeon must decide for himself the procedure in which he is most adept and most familiar. There can be no doubt that in some hands one method may be as good as another. On the other hand, what seems simple and facile to some, may be quite difficult to others. Each surgeon, therefore, must decide on the *modus operandi* best suited to him.

Incision.—At this hospital, the McBurney approach was employed in over 99 per cent of cases of acute appendicitis. Reiteration as to the advantages of this incision over all others, should reveal again the superiority of this approach. Postoperative herniation, even though drainage be resorted to, is minimized. To us, the foremost argument in favor of the gridiron incision is that all manipulation during the operation is effected outside or lateral to

the general peritoneal cavity. This incision affords the surgeon direct approach upon the offending lesion.

The general peritoneal cavity need never be contaminated. One or two sponges applied to the medial aspect of the wound allows for complete exposure and extirpation of the appendix without spreading the infection to the coils of the small intestine—an unfortunate, too frequent concomitant of the right rectus approach.

At all times, manipulation is accomplished in the infected area. No spread of the infection ensues, no matter how extensive the pathologic process encountered. True, at first, there may be difficulty in determining, from one's finger tips, the extent of the inflammation, but just as a master violinist has eyes at his fingers' ends, so too, can the surgeon develop the finesse of tactile acuity that leads one to entertain the thought that surgery is an art as well as a science.

Truly remarkable is the mild postoperative reaction that follows an appendicectomy through a McBurney incision, and that, notwithstanding the severe lesions encountered. Not only is the postoperative convalescence smoother, but also shorter.

Wherever open treatment is indicated, no incision can compare with this invaluable approach, for the abdominal wall almost closes upon itself, as it were, without any sutures.

Too frequently, is the argument propounded that wherever an error in diagnosis be made, the surgeon is handicapped, as well as the patient, in attempting an operation other than appendicectomy through this right McBurney incision. Such was never the contention of McBurney, nor can anyone justify attempting any operation through an improperly placed incision.

There is no reason to prevent any surgeon from closing any improperly placed incision and altering his approach through another, more judiciously placed. No one can justify removing a left ovarian cyst through a right McBurney incision, especially if to the detriment of the patient. To us, the right gridiron incision is indicated only in acute appendicitis, and should never be employed whenever complete exploration is indicated. Adequate exposure is not a virtue of the McBurney incision.

Stump Inversion.—Stump inversion, too, has its many proponents. Many surgeons advocate simple section of the appendicular stump with cauterization or carbolization. We believe such a procedure unphysiologic, since it seems unnatural to allow mucosa to come into contact with serosa. There is no doubt but that such treatment of the stump must carry with it the probability of the formation of more adhesive bands than does the method of tucking in the stump, which results in the apposition of serosal surfaces. Not very long ago, much was written about stump inversion versus stump burial. To us, who have seen thousands of stump inversions following ligation of the stump, the danger of cecal wall abscess is more mythical than real. We have not found ligature of the appendicular stump with inversion, or as some name it, stump burial, an unsafe procedure. However, the added safety, that

stump ligation carries with it a hemostatic adjuvant, cannot be denied. Bleeding into the alimentary canal, a complication almost impossible with stump ligation, is extremely difficult to correct. However, it may be added, that never is stump inversion considered where cecal wall damage has been such as to interdict such practice.

Drainage.—The problem of drainage in acute appendicitis still leaves much to be desired. The old adage of "drain when in doubt" has now swung to "don't drain when in doubt." If one remembers that the general peritoneal cavity cannot be drained, if one is clear that the only purpose of drainage is to allow discharge of pus, and that a drain site is an advantageous guide for the egress of any fecal material that may ensue following damage to the cecum, indications for drainage become apparent.

Every abscess requires drainage; every retroperitoneal appendix should be drained if there is any contamination; every case where the integrity of the cecal wall may be in doubt; every peritonitis where frank pus is expected to ensue; every technically difficult appendicectomy should be drained, if there has been any possible soiling.

Gangrenous appendicitis with clear or turbid nonodorous fluid does not require drainage, nor does a plastic exudate covering the appendix necessitate a drain. However, we cannot agree with those who believe that diffuse peritonitis cases should be closed tightly.

The discussion over the material employed for drains is more academic than practical. We have been using Penrose dam either alone or with gauze. We realize that soft rubber tubing in some hands has acted favorably. The matter of drain removal resolves itself into how long does a drain act as a drain and when does it become a foreign plug? There is no doubt but that 10 days should suffice for the formation of a tract. Too often have we seen a drain removed too late, only to watch ounces of pus follow in the wake of the drain. Too clearly has this demonstrated that drains may block as well as drain a cavity.

Complications.—Complications in acute appendicitis may be classified into two categories, those secondary to the disease entity, and those resultant from the surgeon's intervention.

Acute appendicitis, if allowed to progress unhampered by human intervention, may subside. We fully realize the danger that such a statement may carry to the inexperienced physician, but the fact still remains, and in all fairness should be stated, that there can be no doubt that rare cases of acute appendicitis resolve, some completely, and others pass on into a pathologic *residua* of chronicity. For we know, there are exceptional cases of acute appendicitis where operation, though advised, had been deferred, and yet the patient survived; but those of us who have seen acute appendicitis in its protean manifestations and its chameleon-like diversifications can take but one attitude, and only one, and that is, to excise the offending organ. All the more is this true when we realize that no one can even conjecture which

appendix may burst and which may resolve. Certainly, no one can justify a guess where a human life is at stake.

Acute appendicitis, in the vast majority of instances, if unattended, is more likely to progress in its severity. Suppuration may terminate in necrosis, and gangrene may lead to perforation, which must contaminate the peritoneum, the results of the treatment of which is problematical.

Perforation may result in a localized involvement of the peritoneal cavity or it may be diffuse in its spread. Diffuse peritonitis may also eventually localize in any part of the peritoneal cavity, be it pelvic, subhepatic or subphrenic.

Spread of the infection may not be limited to the peritoneal cavity, for the lymphatic extension into the pleural cage too frequently ensues.

Appendiceal infection may spread not only by contiguity and by lymphatic extension, but frequently also by way of the circulation. Thrombophlebitis of the appendiceal vessels, as a precursor of pyelophlebitis, is well understood. From these beginnings, the organism may then be transplanted through the systemic circulation with all the possibilities that a bacteremia may create.

In addition to this group of complications inherent in appendicitis, there are those sequelae that a surgeon may implant. To be sure, at times, in spite of surgical intervention, complications may ensue as though no therapeusis at all were undertaken. However, such sequelae as hemorrhage, fecal fistulae, herniation, evisceration and many other misfortunes, secondary to human endeavors, require careful consideration. It is our purpose to analyze each of our complications in another communication.

Length of Hospitalization.—Of the 8,539 cases surviving, 4,830 were not drained, and 3,699 were drained. All these cases were studied from the viewpoint of the length of hospitalization (Table XI).

TABLE XI

ANALYSIS OF TIME OF HOSPITALIZATION

No. of Days in Hosp.	Drained	Not Drained
Less than 10 days	153	1,174
10–14 days	1,562	3,193
15–19 days	1,003	329
20–24 days	462	84
25–29 days	241	38
30–34 days	102	13
35 days and over	176	9

Because those cases drained represented complicated or potentially complicated acute appendicitis, over 50 per cent had a period of hospitalization exceeding 15 days, whereas 90 per cent of the undrained cases left the hospital within 14 days after admission.

Mortality.—As previously mentioned, there were 188 deaths in the series. Inasmuch as we intend to deal with these in detail in a subsequent communication, we will but briefly comment on the cause of death. One hundred thirty-one, or 69 per cent of deaths, were due to peritonitis; 11 died

from pulmonary complications; seven deaths were caused by cardiac and cardiovascular complications; 17 deaths were due to embolism; and 22 cases died, because of a variety of causes, which we have grouped as miscellaneous.

SUMMARY

A survey of 8,727 cases of acute appendicitis is presented, with especial reference to mortality rate, age incidence and time element.

The value of early operation is statistically proven by the remarkably low mortality rate in early cases.

The severity of the pathologic process determines the operative procedure; and the degree of peritoneal involvement the difference between low and high mortality results.

The value of the McBurney approach is stressed; and such technical desiderata as stump inversion and drainage are discussed.

Finally, complications are merely classified, with detailed analysis to be carried out in another communication.

These cases comprise all operations for acute appendicitis—private and ward—operated upon by Attending and House Staffs. We wish to thank all those surgeons who have permitted us to include their cases in this report.

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STUDIES OF LIVER FUNCTION BY MEANS OF QUICK'S HIPPURIC ACID TEST*

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Delprat and Whipple,[1] in 1912, were the first to suggest that the determination of hippuric acid excreted after the administration of benzoate might be used as a test for liver function. They did their work on dogs, and advanced their suggestion unaware of the fact that in the dog liver benzoic acid is synthesized in the main to benzoyl-glycuronic acid and not to hippuric acid,[2] as in the case in the human liver. In 1933, Quick[3] introduced his hippuric acid test for liver function in man, and described a simple analytic method for the estimation of hippuric acid in urine, which made the test available for clinical diagnostic purposes. Weichselbaum and Probstein[4] recently modified Quick's method, improving the accuracy of the procedure without impairing its simplicity. By means of the improved method it was ascertained that Quick's statistics represent only partial recovery of the hippuric acid from the urine. It was shown, furthermore, that the losses from solubility of hippuric acid in urine are too variable to give much meaning to Quick's correction for the solubility. In view of this, we deemed it necessary to revise the range of normal values in order to have an adequate basis for comparison when applying the test to patients.

I. Studies on Normal Subjects

Our normal subjects were healthy adults, mainly members of the hospital staff. In the first group of 14 subjects (nine males and five females), 6 Gm. of sodium benzoate were administered as suggested by Quick and, except for the modification in the analytic technic, Quick's procedure was followed in every detail. The findings on this group are shown in Table I.† As may be seen, our subjects eliminated in four hours from 62 to 87 per cent of the ingested sodium benzoate, as compared with 47 to 76 per cent found by Quick[5] in a group of patients who had no clinical evidence of hepatic damage. The average excretion in our group was 73 as against 60 per cent as reported by Quick, or expressed in terms of benzoic acid, healthy individuals excrete in four hours, on an average, 3.7 Gm. of the 6 Gm. ingested, while Quick found an average value of 3 Gm. This substantial difference may be entirely attributed to the improvement upon Quick's method by Weichselbaum and

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† In this table, as well as throughout the paper, the corrected hippuric acid is calculated as its sodium benzoate equivalent, inorder to facilitate the calculation of the amount excreted as the percentage of the amount ingested.

Probstein. However, this difference may to some extent be due to the difference in the selection of subjects for obtaining normal values. We used healthy adult subjects, while Quick used patients without suspected disease of the liver.

TABLE I

EXCRETION OF HIPPURIC ACID BY NORMAL SUBJECTS, OVER A FOUR-HOUR PERIOD AFTER THE INGESTION OF 6 GM. OF SODIUM BENZOATE

Subject	Age	Sex	Urine Volume Cc.	Hippuric Acid Computed as Na-Benzoate Amount in Urine, Gm.	Per Cent of the Na-Benzoate Ingested
S. L.	33	M.	432	5.02	84
T. W.	30	M.	354	4.65	77
W. R.	21	M.	229	4.56	76
D. B.	30	M.	217	4.88	81
R. J.	26	M.	265	4.77	79
D. P.	26	M.	257	4.98	83
R. C.	24	M.	668	5.23	87
H. G.	21	M.	253	4.95	83
M. S.	53	M.	688	4.63	77
H. K.	30	F.	760	4.00	67
A. T.	23	F.	218	4.52	75
A. H.	18	F.	233	3.83	64
C. S.	26	F.	319	3.72	62
M. H.	22	F.	226	3.85	64

It is noteworthy that none of the female subjects eliminated as much as the lowest quantity eliminated by any of the males, the figures being 62 to 75 per cent for the females, and 76 to 87 per cent for the males. In view of the small number of subjects studied, however, we refrain from drawing any conclusions from these figures.

Examining the volume of urine voided during the test, we can find no relationship between the urinary volume and the amount of the hippuric acid excreted. Thus, subject S. L. excreted 5.02 Gm. in 432 cc., and subject D. P. eliminated 4.98 Gm. in 257 cc., while subject H. K., with the largest volume of urine, 760 cc., eliminated only 4 Gm. However, it should be borne in mind that Snapper and Grünbaum[6] observed that patients with nephritis associated with retention of urea may eliminate more hippuric acid in large volumes than in small volumes of urine.

Most of our subjects complained of considerable gastric discomfort, and not a few vomited after taking 6 Gm. of sodium benzoate. Quick[5] suggested the use of smaller quantities whenever the 6 Gm. dose causes vomiting. We regarded it desirable to examine the possibility of using smaller quantities of benzoate as the general standard dose.

Accordingly, we performed the test with 4 Gm. doses on 24, and with 3 Gm. doses on 23 normal subjects. The procedure was otherwise the same as with the 6 Gm. dose, the hourly elimination of hippuric acid being determined for four hours. We found that either of the two smaller doses was

much better tolerated than the 6 Gm. dose. To further determine the possibility of using either of the smaller doses, it became necessary to analyze our results in order to learn whether or not the smaller doses are capable of taxing the ability of the liver to synthesize hippuric acid at the same maximum rate at any single hour in the course of the observation as the 6 Gm. dose. To this end, we determined the hourly excretion of hippuric acid on seven of our subjects after the ingestion of the three different doses. It was found that the maximum excretion was, without exception, attained in the second hour after the 4 Gm., and in either the second or third hour after the 6 Gm. dose. In Table II these maximum excretions for one hour are compared for the seven subjects.

TABLE II

MAXIMUM HOURLY EXCRETION OF HIPPURIC ACID AFTER INGESTION OF VARIABLE AMOUNTS OF SODIUM BENZOATE

Subject	Maximum Hourly Excretion of Hippuric Acid After Ingestion of 6 Gm.	4 Gm.	3 Gm.
S. L.	1.40	1.37	1.27
W. R.	1.34	1.34	1.21
H. G.	1.71	1.40	1.27
T. W.	1.38	1.35	1.14
M. S.	1.40	1.41	1.11
R. P.	1.49	1.51	1.25
M. H.	1.12	1.36	1.09
Average	1.40	1.39	1.19

It may be seen that the maximum hourly rate was the same after the 6 and 4 Gm. doses, whereas the 3 Gm. dose was not sufficient to call forth a similar maximum response. This finding indicates that the maximum hourly excretions obtained after the 4 and the 6 Gm. doses represent the maximum hourly rate of hippuric acid synthesis in the liver under the given standard conditions. Raising the dose above 4 Gm. does not lead to an increase of this maximum hourly rate, although the total excretion for four hours may be augmented. We have even a few cases in which the highest excretion during any single hour is less with the 6 than with the 4 Gm. dose.

TABLE III

COMPARISON OF OPTIMUM HOURLY EXCRETION OF HIPPURIC ACID IN DIFFERENT SUBJECTS FOLLOWING INGESTION OF VARIABLE AMOUNTS OF SODIUM BENZOATE

	Optimum Hourly Rate of Hippuric Acid Excretion After Ingestion of 6 Gm. (13 Subjects)	4 Gm. (24 Subjects)	3 Gm. (23 Subjects)
Lowest	1.04	1.06	0.98
Highest	1.92	1.80	1.41
Average	1.38	1.39	1.19

In Table III the extreme and average values of the maximum hourly excretions in all the subjects studied are recorded in groups arranged according

to the dose of benzoate ingested. Here it is demonstrated on a large number of subjects that the range of variation as well as the average values in regard to the maximum hourly rate are essentially the same for the 6 and the 4 Gm. doses. The average for 6 Gm. is 1.38 and that for 4 Gm. is 1.39. The 3 Gm. dose falls short of eliciting a similar response, evidently because at no time does it furnish to the liver a concentration of benzoic acid that would suffice for the possible maximum velocity in the synthetic reaction. On the ground of the foregoing, it can be stated that the 4 Gm. dose is large enough to give the liver an opportunity to synthesize hippuric acid at its maximum capacity during one hour. In healthy individuals a maximum of from 1.38 to 1.92 Gm. of sodium benzoate can be synthesized to hippuric acid in the course of one hour. This maximum cannot be raised by increasing the dose above 4 Gm.

TABLE IV

RATE OF EXCRETION OF HIPPURIC ACID IN NORMAL SUBJECTS AFTER INGESTION OF 4 GM. OF SODIUM BENZOATE

Subject	Age	Sex	Per Cent Excreted During First Hour	Second Hour	Third Hour	Fourth Hour	Total in Four Hours
1. L.	33	M.	28	34	25	7	94
2. W. R.	21	M.	23	33	25	10	91
3. P.	21	M.	38	31	12	4	85
4. S.	22	M.	23	31	24	9	87
5. B.	30	M.	19	45	19	3	86
6. G.	21	M.	28	35	17	4	84
7. C.	21	M.	28	37	18	4	87
8. W.	30	M.	25	34	28	5	92
9. M. S.	53	M.	27	35	21	9	92
10. S. 2	19	M.	21	31	30	9	91
11. A.	24	M.	28	37	19	5	89
12. R.	28	M.	32	36	19	4	91
13. H.	32	M.	21	31	28	6	86
14. M. H.	18	F.	28	37	19	3	87
15. Z.	29	F.	21	29	27	12	89
16. M. L. H.	22	F.	18	34	23	5	80
17. M. K.	32	F.	29	33	23	8	93
18. R. L.	28	F.	23	30	27	8	88
19. P. 2	40	F.	26	48	13	3	90
20. K.	35	F.	36	41		20*	97
21. S. 3	25	F.	26	35	21	7	89
22. T.	24	F.	22	33	24	6	85
23. C.	27	F.	14	41	29	2	86
24. T. 2	26	F.	24	26	22	11	83
Lowest			14	26	12	3	80
Highest			38	48	30	12	97
Average			25	35	22	6	88

* Combined excretion for third and fourth hours.

We conclude then that 4 Gm. of sodium benzoate is the ideal dose to be used for the Quick test. Because of this, we give in Table IV in some detail our findings in 24 normal subjects (13 males and 11 females) who have taken this dose. The total excretion of hippuric acid (computed as sodium benzoate) for four hours ranges from 80 to 97 per cent of the ingested sodium benzoate, with an average of 88 per cent. There is no appreciable difference between the sexes. The curve of the hourly rate of excretion for the four-hour period is of a uniform character for all the subjects. Thus in all but one instance, the highest level of hippuric acid elimination was observed in the second hour; 50 to 77 per cent of the ingested sodium benzoate was handled during the first two hours; while the level of excretion during the third and fourth hours depended upon the quantity of the hippuric acid that had been eliminated in the preceding periods, in that the excretion in the last two hours tended to be the higher, the lower the excretion in the first two hours had been.

Since 4 Gm. of sodium benzoate is the smallest dose administered by mouth that is capable of showing the maximum rate at which the liver is able to synthesize hippuric acid, in those instances in which the 4 Gm. is followed by vomiting, the sodium benzoate must be administered intravenously, as recently suggested by Quick, Ottenstein and Weltcheck.[7]

TABLE V

EFFECT OF ADMINISTRATION OF SODIUM BENZOATE PLUS GLYCINE TO NORMAL SUBJECTS ON THE EXCRETION OF HIPPURIC ACID

Subject	Excretion of Hippuric Acid (in Terms of Na-Benzoate)			
	4 Gm. of Na-Benzoate		4 Gm. of Na-Benzoate + 5 Gm. of Glycine	
	Grams	Per Cent of Ingested Benzoate	Grams	Per Cent of Ingested Benzoate
1	1.08	27	2.05	51
2	0.94	23	1.65	41
3	1.05	26	2.02	50
4	1.13	28	2.13	53
5	1.01	25	2.09	52
Average	1.04	26	1.98	49

Quick[8] made the observation that the fundamental factor governing the rate of synthesis (and subsequent excretion) of hippuric acid is the rate at which the liver is able to furnish glycine. Thus by administering glycine simultaneously with benzoate, the rate of elimination of hippuric acid can be increased. We have repeated this experiment by administering 5 Gm. of glycine with 4 Gm. of sodium benzoate to five subjects. Our findings, recorded in Table V, confirm Quick's observation. It may be seen that the excretion of hippuric acid during the first hour was practically doubled when 5 Gm. of glycine was administered together with the sodium benzoate.

In another experiment, by administering increasing quantities of glycine with 6 Gm. of sodium benzoate to two normal subjects, we attempted to determine the maximum ability of the liver to conjugate glycine with benzoic

TABLE VI

MAXIMUM CAPACITY OF THE LIVER TO PRODUCE HIPPURIC ACID, AND THE AMOUNT OF GLYCINE REQUIRED FOR THIS PURPOSE

Subject	Dose Ingested		Hippuric Acid Excreted During Consecutive 15-Min. Periods						Hippuric Acid Excreted During 90 Mins.
	Glycine	Na-Benzoate	1	2	3	4	5	6	
S. L.	1.5 Gm.	6 Gm.	.21	.36	.50	.54	.60	.52	2.73
	3.0 Gm.	6 Gm.	.16	.45	.60	.77	.61	.74	3.33
	4.5 Gm.	6 Gm.	.15	.47	.61	.69	.69	.77	3.38
	6.0 Gm.	6 Gm.	.14	.46	.70	.71			
E. S.	1.5 Gm.	6 Gm.	.09	.27	.33	.35	.39	.39	1.82
	3.0 Gm.	6 Gm.	.00	.32	.38	.47	.46	.56	2.19
	4.5 Gm.	6 Gm.	.12	.36	.51	.62?	.72	.76	3.09?
	6.0 Gm.	6 Gm.	.18	.47	.66	.79	.74	.78	3.62

Note: The first three mixtures to each subject were given in divided doses, *i.e.*, two-thirds of the dose of each of the ingredients was given at the beginning of the test, and one-third one-half hour later.

acid when both constituents were available in unrestricted amounts. The results of this experiment are shown in Table VI. We started out with a mixture containing approximately one-half the molecular equivalent of glycine to the molecular equivalent of sodium benzoate, and then increased the glycine to one, one and one-half, and two molecular equivalents. In subject S. L. the maximum rate of synthesis was reached with the mixture containing molecular equivalents of glycine and sodium benzoate, while in subject E. S. it was reached with one and one-half molecular equivalents of glycine. In the two subjects the maximum amount of hippuric acid synthesized in 90 minutes amounted to 3.38 and 3.62 Gm., respectively, far more than without the feeding of glycine. The largest output was 0.79 Gm. in 15 minutes, which corresponds to an hourly rate of 3.16 Gm., as against 1.92 Gm., which was the highest rate observed after the ingestion of 6 Gm. of sodium benzoate but without the addition of glycine (see Table III).

CONCLUSIONS

(1) After the ingestion of 6 Gm. of sodium benzoate, 12 healthy adult subjects eliminated 62 to 87 per cent of the ingested benzoate in four hours, with an average of 73 per cent. This is an average of 3.7 Gm. in terms of benzoic acid as compared with 3 Gm., Quick's normal average.

The analytic method used for the estimation of hippuric acid in urine was the Weichselbaum-Probstein modification of Quick's method; the greater accuracy of the modified method accounts for the higher values in our experiments.

(2) Four grams of sodium benzoate is the ideal dose to be used for liver function tests, since it is as fully capable of gauging the maximum rate at which the liver is able to synthesize hippuric acid as Quick's 6 Gm. dose, at the same time causing far less gastric discomfort than the 6 Gm. dose.

(3) Twenty-four normal subjects who ingested 4 Gm. of sodium benzoate eliminated 80 to 97 per cent of the drug in four hours, with an average of 88 per cent. The curve of the hourly rate of excretion is of a uniform character, the peak of excretion being reached during the second hour; 50 to 77 per cent of the sodium benzoate was handled during the first two hours.

(4) The rate of hippuric acid excretion during the first hour after the ingestion of sodium benzoate was doubled in four out of five subjects after the administration of glycine with the sodium benzoate.

(5) The maximum quantity of hippuric acid which could be synthesized when an adequate supply of both glycine and benzoic acid was available was 0.77 and 0.79 Gm. (in terms of sodium benzoate), respectively, in a 15-minute period in two normal subjects.

II. Studies on Patients

To date, we have applied the hippuric acid test, with the 4 Gm. dose of sodium benzoate, to 103 patients, representing a variety of diagnoses, some of them tentative. The results were compared with the normal values described in the preceding chapter. On this basis it is assumed that in patients who in the course of four hours excrete less than 80 per cent of the ingested sodium benzoate, *i.e.*, less than the minimum excreted by normal individuals (see Table III), the liver function is impaired. Interpretation of the results is simple enough when the excretion is substantially below 80 per cent; it is difficult, however, to base conclusions upon figures that are near the border line. Yet these are just the cases which deserve greatest attention from the point of view of diagnosis. After all, when the liver function is shown by the test to be severely damaged, the test as a rule merely serves to confirm clinical observation and judgment; but a value of a much higher order consists in the detection of pathologic processes at such early stages where other approaches fall short.

Guided by this point of view, we attempted to carry out the hippuric acid test in a form which might permit a finer analysis and more satisfactory interpretation of the results in the border line cases. This is the reason why we placed the emphasis upon the hourly fractions of the hippuric acid excretion rather than the total of the four-hour period. Two figures in such fractional determinations proved to be enlightening. One is the time of appearance of the maximum amount excreted in a single hour; in normal subjects this amount appears almost invariably in the second-hour interval (Table III). The other figure is the sum of the two quantities excreted during the first and the second hours; this in normal subjects may be as high as 77 per cent, but always is at least 50 per cent. Now, in distinctly pathologic cases in which the total excretion during four hours is well below 80 per cent, the maximum hourly excretion may appear in any one of the four hourly intervals, and the sum of the excretion during the first two hours is considerably below 50 per cent. In border line cases, in which the total excretion closely approaches, and occasionally even slightly overlaps, the lowest limit of the normal, the maximum hourly excretion often shifts to the third hourly interval, and the sum of the two quantities ex-

creted during the first and second hours is always less than 50 per cent of the ingested benzoate. There are other border line cases in which the sum of excretion for the first two hours is 50 per cent or more, yet the level of excretion during the last two hours falls so abruptly that the total for four hours falls substantially below 80 per cent. These types of cases we consider as pathologic border line cases.

Inasmuch as the great majority of pathologic cases excrete less than 50 per

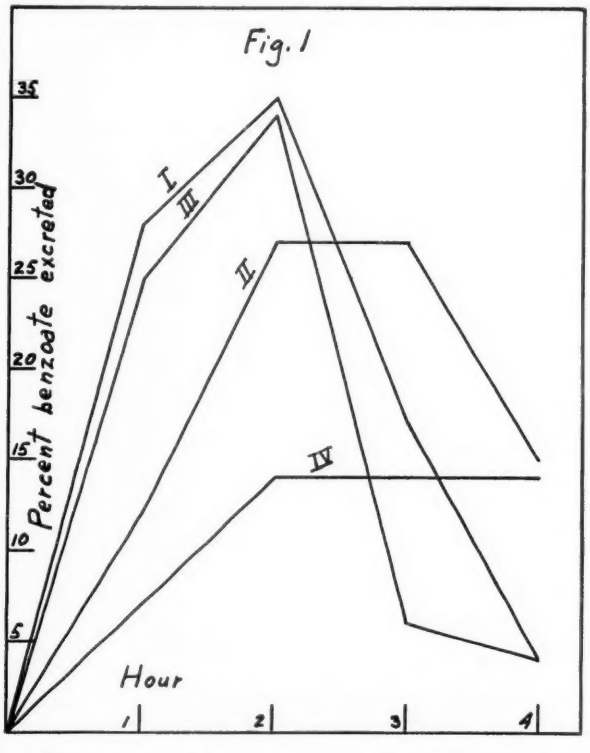

FIG. 1.—Curve I. Normal subject. No. 6, Table IV: Total elimination, 84 per cent. Curve II. Border line case. Patient No. 16, Table VIII: Total elimination, 81 per cent. Curve III. Border line case. Patient No. 26, Table IX: Total elimination, 69 per cent. Curve IV. Definite impairment. Patient No. 4, Table VII: Total elimination, 49 per cent.

cent (our lowest normal) in the first two hours, we feel that for most clinical purposes the test need be run for only two hours. A single determination of hippuric acid in a two-hour specimen is all that is necessary, with 50 per cent excretion being regarded as the lower limit of normal.

The relationships just pointed out are illustrated in Figure 1. Curve I represents a normal case (No. 6 in Table III) with a total excretion of 84 per cent in the course of four hours, a figure that is near the lower limit of normal values. Curve II is a border line case (No. 16 in Table VIII) in which the total excretion in four hours was 81 per cent, a figure that reaches up into the range of normal values; the excretion for the first two hours, however, was only 39 per cent, as against at least 50 per cent in normal cases. It may be

stated that this test was performed ten days after a cholecystectomy; a subsequent test, one week later, yielded normal values both as regards the hourly rate of excretion and the total for four hours. The other type of border line case is illustrated by Curve III. Here we have a patient (No. 26 in Table IX) who excreted 59 per cent, that is to say a normal quantity, during the first two hours; yet there was such a marked drop during the last two hours that the total excreted in four hours was only 69 per cent. Finally, Curve IV, representing a definitely pathologic case (No. 4 in Table VII), with a total excretion of 49 per cent, is included for comparison with the other three curves.

TABLE VII

HIPPURIC ACID TEST IN LIVER DISEASES

No.	Patient	Age	Sex	Diagnosis and Remarks	Blood NPN	Per Cent of Ingested Na-Benzoate Excreted During First Hour	Second Hour	Third Hour	Fourth Hour	Total in Four Hours
1	E. A.	31	F.	Cirrhosis	19	9	3	7	7	26
2	M. B.	56	F.	Cirrhosis	14	1	9	14	14	38
3	H. S.	55	M.	Cirrhosis (biopsy)	20	19	32	24	7	82
4	J. F.	55	M.	Cirrhosis (biopsy)	24	7	14	14	14	49
5	P. C.	43	F.	Possible cirrhosis, icterus	14	5	No spec.	18	5	28
6	M. Y.	60	M.	Portal cirrhosis (?) Malignancy (?) Ascites, abdominal mass	18	7	12.	11	10	40
7	N. C.	51	F.	Hepatosplenomegaly, cirrhosis (?)	14	20	20	18	10	68
8	L. B.	64	F.	Hepatomegaly, icterus. Wassermann ++++		10	13	27	10	60
9	L. S.	56	F.	Hepatomegaly, icterus. (Malignancy of bone?)	18	5	9	17	18	49
10	H. C.	49	M.	Hepatomegaly (cirrhosis). Test after prostate operation	28	30	12	12	18	72
11	M. B.	68	F.	Hepatomegaly, proliferative arthritis	15	10	23	27	13	73
12	L. F.	52	F.	Hepatosplenomegaly, gastric hemorrhages	15	29	44	14	2	89
13	A. T.	48	M.	Small liver, icterus (cause unknown)	16	10	23	15	21	69
14	R. E.	18	M.	Catarrhal jaundice	18	12	17	9	--	38 (3 hrs.)
15	B. L.	27	M.	Catarrhal jaundice (3 days)	22	13	21	5	6	45
16	F. H.	30	M.	Arsenical hepatitis	20	20	21	24		65 (3 hrs.)
17	J. B.	38	M.	Arsenical hepatitis (?)	38	30	12	12	18	72
18	R. T.	49	M.	Subsided arsenical hepatitis, hepatomegaly still present	22	23	9	10	11	53

Of the 103 patients examined, 18 were diagnosed as suffering from various liver diseases. The results of the tests, presented in Table VII, show that all but two had a distinctly diminished capacity to synthesize hippuric acid. One (No. 4) of the exceptions was a case of cirrhosis, the other (No. 12) one of hepatomegaly.

In Table VIII are recorded 17 cases with biliary tract and gallbladder diseases. Of these, all but three showed distinctly an impairment of liver function. In two cases (Nos. 11 and 15) the hippuric acid was produced at the normal rate, while two cases (Nos. 13 and 16) gave border line results. It is interesting that all the cases of biliary tract obstruction showed impairment of the liver function.

TABLE VIII

HIPPURIC ACID TEST IN BILIARY TRACT AND GALLBLADDER DISEASES

No.	Patient	Age	Sex	Diagnosis and Remarks	Blood NPN	Per Cent of Ingested Na-Benzoate Excreted During First Hour	Second Hour	Third Hour	Fourth Hour	Total in Four Hours
1	S. W.	49	M.	Stenosis of common duct or common duct stone. Jaundice, chills	14	18	27	20	9	74
2	M. S.	69	F.	Stenosis of common duct, icterus.						
				6/9/38	18	11	22		17*	50
				9/7/38		12	12	13	10	47
				4 wks. after anastomosis of common duct to jejunum.						
				10/6/38		15	16	25	19	75
3	F. B.	36	F.	Stricture of common duct.						
				5/19/38	16	18	10	25	18	71
				6/10/38		20	28	21	8	77
				1/6/39		9	22	24	12	67
				1/14/39—1 wk. of high CH.-low fat diet		21	28	19	7	75
4	M. S.	50	M.	After operation for stricture of common duct. Patient still icteric.	23	17	20	23	6	66
				Repeated after icterus subsided		12	21	27	12	72
5	G. D.	71	M.	Common duct stone (?), carcinoma of pancreas (?).	23	0	10	11	8	29
				After 8 days of high CH. diet		4	24	9	13	50
6	W. C.	31	M.	Recurrent obstructive jaundice	31	21	22	26	6	75
7	C. B.	52	F.	Stenosis of common duct, icterus	20	13	13	15	22	63
8	J. C.	71	M.	Obstructive jaundice. Probable carcinoma head of pancreas	20	0	15	21	—	36 (3 hrs.)
9	N. L.	33	M.	Repeated attacks of pain in right upper quadrant. Diagnosis (?)	18	10	27	25	14	76
10	F. S.	43	F.	Cholecystitis, pituitary obesity	20	20	25	17	8	70
11	E. G.	50	M.	Chronic cholecystitis, osteoarthritis	16	51 (90 min.)	18 (next 30 min.)	13	6	88
12	L. G.	34	F.	Chronic cholecystitis	16	9	21	29	8	67
13	E. W.	40	F.	Cholecystitis (?); high blood cholesterol	20	9	34	16	21	80
14	S. H.	47	F.	3 wks. after operation for gallstones and hydrops of gallbladder	13	19	28	23	—	70(3 hrs.)
15	T. P.	28	F.	12 days after cholecystectomy	13	32	25	24	4	85
16	M. R.	56	M.	Acute cholecystitis.						
				10 days after operation.	21	12	27	27	15	81
				17 days after operation		20	33	20	11	84
17	F. S.	29	F.	Acute gangrenous cholecystitis.						
				10 days after operation.	15	6	26	16	6	54
				17 days after operation		23	33	15	8	79

* Combined excretion for third and fourth hours.

Table IX contains 26 cases with a variety of diseases which show impaired liver function. It may be noted that in diabetes, in several forms of arthritis, in hyperthyroidism, and in cardiac diseases some of the patients showed impaired liver functon, while others had normal liver function so far as the ability to produce hippuric acid is concerned.

In some cases repetition of the hippuric acid test proved to be of value in demonstrating changes in the condition of the liver. In the chart which comprises Figures 2 to 5, the improvement of the liver function is shown in the form of hourly rate curves of hippuric acid excretion. Figure 2 is the graphic

presentation of Case No. 2 of Table VIII, showing the substantial recovery of liver function three weeks after surgical operation for stenosis of the common duct. Figure 3 (Case No. 5 in Table VIII) illustrates a distinct improvement as a result of dietary regulation. Figure 4 illustrates the return of impaired liver function to normal five days after a marked sulfanilamide reaction, and Figure 5 exhibits a similar picture six weeks after aniline poisoning. Table VIII contains a few more similar results after surgical operations in diseases of the gallbladder and of the biliary tract.

TABLE IX

MISCELLANEOUS DISEASES SHOWING IMPAIRED LIVER FUNCTION

No.	Patient	Age	Sex	Diagnosis and Remarks	Blood NPN	Per Cent of Ingested Na-Benzoate Excreted During First Hour	Second Hour	Third Hour	Fourth Hour	Total in Four Hours
1	M. H.	50	M.	Diabetes mellitus†		20	20	25	12	77
2	P. E.	64	M.	Diabetes; gangrene of foot	16	28	36	6	3	73
3	B. F.	49	F.	Diabetes; marked hypercholesteremia	15	4	27	6	9	46
4	P. R.	60	M.	Arthritis‡	23	2	38	19	9	68
5	H. G.	60	F.	Proliferative arthritis; gout	22	16	25	30	7	78
6	L. A.	41	M.	Spondylosis	15	18	42.	11	2	73
7	C. P.			Degenerative arthritis; iritis	22	17	28	25	10	80
8	E. S.	49	F.	Proliferative arthritis	16	15	12	15	22	64
9	M. G.	10	F.	Proliferative arthritis; obesity	23	10	16	16	14	56
10	M. L.	23	F.	Hyperthyroidism; B.M.R.+45	16	15	§	15*	21	51
11	A. J.	56	F.	Hyperthyroidism; B.M.R.+21	20	4	25	23	17	69
12	B. M.	36	F.	Hyperthyroidism; B.M.R.+2	18	20	23	24	8	75
13	E. O.	66	M.	Hypertensive heart disease‖	23	13	21	10	23	67
14	C. C.	58	M.	Degenerative heart disease	17	10	6	23	18	57
15	M. L.	76	F.	Hemorrhage into thyroid (?)	31	0	0	0	0	0
16	M. G.	50	F.	Chronic pancreatitis	15	4	7	8	5	24
17	E. S.	14	F.	Residual poliomyelitis	17	12	5		3*	20
18	S. F.	36	F.	Sciatica	21	22	41		5*	68
19	C. K.	37	F.	Undulant fever	13	10	11	15	6	42
20	H. L.	59	M.	Xanthomatosis; hypercholesteremia	22	22	30	15	7	74
21	M. F.	26	F.	Hypercholesteremia	20	19	5	28	14	66
22	J. S.	31	M.	Marked reaction to sulfanilamide	17	15	16	14	12	57
23	M. G.	14	M.	Aniline dye poisoning		10	16	26	15	67
24	T. L.	54	F.	Carcinoma of the colon, no liver metastasis	18	23	23	21	8	75
25	F. M.	56	M.	Asthma	18	20	31	16	7	74
26	H. C.	33	M.	Syphilis; pachymeningitis hemorrhagica	16	25	34	6	4	69

* Combined excretion for this and preceding hour.
† In three other diabetics, the test gave normal results.
‡ In 11 other cases of arthritis, the results were normal.
§ In two other cases of hyperthyroidism, the results were normal.
‖ In two other cases of hypertensive heart disease, results were normal.

Attention has been directed to the influence of renal function upon the result of the hippuric acid test. Deficient renal function may depress the rate of excretion of hippuric acid and, thereby, a picture may result which indicates impaired liver function. Some workers regarded it necessary, therefore, to ascertain in doubtful cases that renal function is normal, by performing urea clearance tests together with the hippuric acid test. However, Quick[5] said that

the rate of hippuric acid excretion by the kidneys is 50 per cent higher than the rate of the synthesis of that compound in the liver, and that, as a consequence, only very serious disorders in kidney function could affect the elimination of hippuric acid. Snapper and Grünbaum[6] observed hippuric acid retention in nephritic patients only when retention of urea was demonstrable. On examination of the tables in the paper of Fouts, Helmer and Zerfas,[9] one finds instances in which the rate of excretion of hippuric acid is normal despite greatly diminished urea clearance.

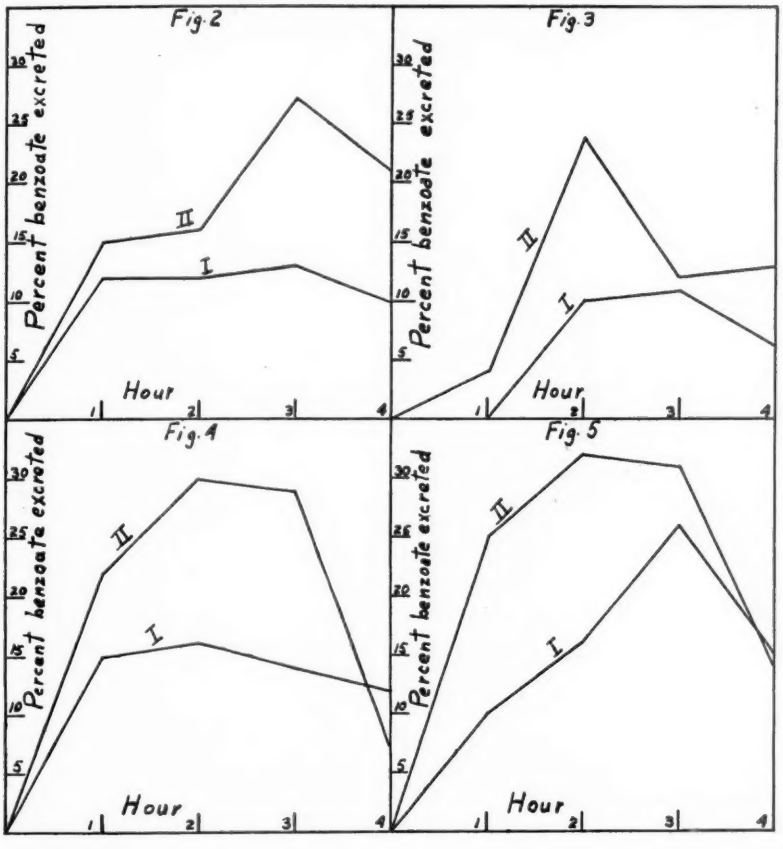

FIG. 2.—Stenosis of common duct: Curve I, before operation. Curve II, improvement four weeks after operation.

FIG. 3.—Obstructive jaundice, due to common duct stone, or carcinoma of the head of the pancreas: Curve I, soon after the patient's admission to the hospital. Curve II, improvement following eight days of high carbohydrate diet.

FIG. 4.—Sulfanilamide reaction: Curve I, during reaction to drug. Curve II, normal test during recovery.

FIG. 5.—Aniline dye poisoning: Curve I, test while patient was ill. Curve II, several weeks after patient's discharge from the hospital.

In considering this question we have borne in mind that Van Slyke and his coworkers[10] have shown that only when urea clearance is 50 per cent or less do we begin to find cases with retention of urea, and that only when the urea clearance is 20 per cent or less do all cases show a retention of urea. In view

of these facts, and of Snapper and Grünbaum's observation, we are not surprised to find that there is no constant correlation between reduced urea clearance and diminished excretion of hippuric acid. Thus we see in Table X,

TABLE X

EFFECT OF IMPAIRED KIDNEY FUNCTION UPON THE EXCRETION OF HIPPURIC ACID

No.	Patient	Age	Sex	Diagnosis	Urea Cl. Per Cent	Blood Urea N	Per Cent of Ingested Na-Benzoate Excreted During First Hour	Second Hour	Third Hour	Fourth Hour	Total in Four Hours
1	A. W.	24	F.	Chronic nephritis	30	14		39*	29	14	82
2	M. B.	54	F.	Kidney damage following transfusion reaction	40	12	20	34	24	11	89
3	C. W.	51	M.	Proliferative arthritis	53	13	23	35	23	5	86
4	S. S.	52	F.	Proliferative arthritis	41	14	26	27	24	5	82
5	F. J.	58	M.	Gout	57	14	17	31	21	12	81
6	F. A.	68	M.	Acute infectious arthritis	33	31	22	35	17	7	81
7	J. F.	45	M.	C.N.S. syphilis		20	26	27		32*	85
8	M. L.	49	M.	Bronchial asthma		28	22	23	26	8	79
9	D. J.	55	M.	Gangrene of feet		28	0	7	6	1	14
10	C. T.	56	M.	Hypertensive heart disease		21	5	15	18	18	56
11	H. H.	51	M.	Cardiorenal		20	0	3	3	6	12
12	M. B.	46	F.	One kidney	19	22	10	16	16	7	49
13	F. G.	63	F.	Gout; arteriosclerosis		22	17	26	5	7	55
14	D. A.	60	M.	Cardiorenal		110	0	0	0	0	0

The urea N values in the patients who did not have urea clearance tests were calculated from the NPN values determined on zinc filtrates of blood according to the method of Somogyi.[11] According to his figures, the upper limit of normal blood urea is 19 mg. per cent.

* Combined excretion for this and preceding hour.

which contains the results of the hippuric acid test in patients with various degrees of impairment of kidney function, that patients Nos. 1 to 5 with urea clearances of 30 to 57 per cent, but with normal values for blood urea, all show normal values in the hippuric acid test. On the other hand, patients Nos. 9 to 14, with varying degrees of urea retention, all show diminished excretion of hippuric acid; patient No. 14 of this group, with a urea nitrogen of 110, did not excrete any hippuric acid at all during the entire four hours. But even in some of these instances we cannot say that the impaired renal function is responsible for the diminished hippuric acid excretion, since patients Nos. 6 to 9 give normal or near normal responses to hippuric acid tests, despite increased urea contents in the blood.

Taking these observations into consideration, we are persuaded that only in the presence of marked diminution of renal function which is associated with increased urea content of the blood is the excretion of hippuric acid affected by the renal factor. It is, therefore, unnecessary to perform the urea clearance test for the proper interpretation of the hippuric acid test. Knowledge of the urea or nonprotein nitrogen content of the blood suffices, and only when these are higher than normal need the interpretation of low hippuric acid output be in doubt.

A question which merits consideration concerns the factor or factors which cause the diminution of hippuric acid formation in the liver in pathologic cases.

Quick[5] believes that the reduction is due primarily to a diminished capacity of the liver to synthesize glycine, and in part to damage of the enzymatic mechanism which unites benzoic acid with glycine. We inquired into this question by administering 5 Gm. of glycine plus 4 Gm. of sodium benzoate to six patients who had previously been found to have definitely decreased capacity to produce hippuric acid when they were given sodium benzoate only. In Table XI it

TABLE XI

RESPONSE TO ADMINISTRATION OF GLYCINE PLUS SODIUM BENZOATE IN PATIENTS SHOWING AN IMPAIRMENT OF LIVER FUNCTION BY THE HIPPURIC ACID TEST

No.	Patient	Diagnosis	Remarks	Per Cent of Ingested Na-Benzoate Excreted During				Total in Four Hours
				First Hour	Second Hour	Third Hour	Fourth Hour	
1	M. S.	Stricture of common duct	Without glycine.	16	20	23	6	65
			With glycine	30	45	12	4	91
2	M. L.	Hyperthyroidism	Without glycine.		15*	15	21	51
			With glycine	26	42		14*	82
3	B. S.	Stenosis of common duct	Without glycine.	12	12	13	10	47
			With glycine	27	32	20	6	85
4	J. F.	Portal cirrhosis	Without glycine.	7	14	14	14	49
			With glycine	3	23	16	8	50
5	A. T.	Small liver, jaundice	Without glycine.	11	14	22	16	63
			With glycine	10	14	20		44 (3 hrs.)
6	E. S.	Proliferative arthritis	Without glycine.	15	12	15	22	64
			With glycine	45	36	7	3	91

* Combined excretion for this and preceding hour.

can be seen that only patient No. 6 responded as did our normal subjects to the addition of glycine to the test (*cf.* Table V), in that this patient was able to excrete 45 per cent of the ingested benzoate during the first hour when glycine was added. In this instance, one can say that the impairment of liver function concerned mainly the diminished capacity of the liver to furnish glycine. On the other hand, although patients Nos. 1 to 3 responded with an increased elimination of hippuric acid when glycine was added, this increase was considerably smaller during the first hour than was observed in any of our normal subjects under similar conditions. In these instances a definite slowing down of the rate of the conjugation process as well as in the production of glycine occurred. Finally, patients Nos. 4 and 5 showed no response at all to the administration of glycine, indicating a marked impairment of the enzymatic mechanism which unites benzoic acid with glycine.

From these observations it may be concluded that in some patients the main defect consists in the diminished ability of the liver to furnish glycine, while in others the enzymatic conjugation process is defective. The two deficiencies may be present simultaneously. By performing the double test as was done in these six patients, it may be possible to gauge two distinct liver functions, namely, glycine synthesis, and the conjugation of benzoic acid with glycine. Further observations will be necessary before the merits of such double tests can be evaluated.

CONCLUSIONS

(1) For Quick's liver function test, 4 Gm. of sodium benzoate as the standard dose is superior to the 6 Gm. dose.

(2) Estimation of the hippuric acid excretion at hourly intervals, in addition to determination of the total amount eliminated during the course of four hours, enhances the values of the test in that it permits evaluation of the degree of severity of the liver impairment.

On this basis we classify the cases as follows:

(a) Marked or severe impairment where both the total elimination and the maximum excretion in a single hour (maximum hourly rate) are subnormal.

(b) Mild degrees of impairment, where the total hippuric acid eliminated in four hours is but slightly depressed or is a low normal, but where the amount eliminated in the first two hours is below 50 per cent of the ingested benzoate.

(c) Borderline cases, in which the elimination in the first two hours is 50 per cent or more, but in which the total elimination for the entire period is somewhat depressed.

The lines of demarcation between these three groups are, of course, not sharp.

(3) On the basis of our tabulated results we consider an abbreviation of the test to a two-hour period as quite satisfactory for most clinical purposes. In this form of the test, the analytic work is reduced to a single determination of hippuric acid in the total urine excreted during two hours. If the hippuric acid excreted in two hours represents 50 per cent or more of the ingested 4 Gm. of benzoate, this may be accepted as a sign of normal liver function in respect to the process involved.

(4) The usefulness of the test is not affected by impaired renal function unless this attains such a degree of severity as to be associated with retention of urea.

(5) A few of our experiments indicate that, whereas, subnormal results in the hippuric acid test are to be ascribed mainly to a deficiency in the ability of the liver to supply glycine at a normal rate, there are cases in which the main cause may be ascribed to a deficiency in the mechanism responsible for the conjugation of benzoic acid with glycine.

We are indebted to Dr. Avery Rowlette and the resident staff of the St. Louis City Hospital for furnishing us some of our cases.

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STUDIES ON THE CAUSE OF DEATH IN TETANUS*

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IN 1903, Meyer and Ransom[1] reported some experiments upon cats and rabbits in which large and rapidly fatal doses of tetanus toxin were injected into the substance of the lumbar segment of the nontransected spinal cord. These and other experiments[2] of Meyer's were carefully repeated upon dogs, in 1935, by Firor and Jonas.[3] They were able to show, as Zupnik[4] had suggested in 1902, that spinal injections of toxin can produce tactile reflex motor tetanus without inducing any sign of the muscular rigidity which complicated Meyer's experiments and fortified his belief that both the muscular rigidity and the reflex convulsions of tetanus were of solely central origin. In repeating Meyer's experiments the amount of toxin injected into any one dog's lumbar cord (a nonvital center) was very much smaller (1/4 to 1/150) than the amount required to kill the animal had the toxin been injected intravenously, subcutaneously, or intramuscularly. And yet in each of the 11 experiments the dog died within a week. It was this unexpected and early death which first gave rise to the suspicion that tetanus toxin may be altered when in contact with the cells of the spinal cord.

In an attempt to confirm our suspicions, we carried out the experiments described in a paper published in 1938, entitled "The Apparent Alteration of Tetanus Toxin Within the Spinal Cord of Dogs."[5] We related there the facts which led us to entertain the possibility of such alteration. In order to establish without any doubt the pattern of reaction for each experiment reported in that paper, we have enlarged our series in each category. The present paper tabulates these experimental results to date. We were also anxious to find more definite proof, or disproof, of the apparent alteration of the toxin. Our further attempts, together with some related experiments, occupy the latter part of this communication.

To avoid too much repetition we have omitted from this paper the complete descriptions of *Methods of Procedure* and the *Protocols of Typical Experiments* that appeared in our earlier paper; and in an effort to clarify the discussion we have altered somewhat the order in which the various experiments were presented in the previous paper. However, to facilitate reference to the more detailed descriptions of procedures, we have indicated in parentheses under each experiment in the present paper the corresponding sections of our earlier paper.

Notes on Dosage, Toxins, Abbreviations Used in the Tables, Symptoms, etc.—Although in keeping our records and in calculating our doses our standard unit was the guinea-pig median lethal dose (or LD50), we have in this paper expressed our doses as

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multiples or fractions of a lethal dose for the animal concerned. Our lethal dose is the minimum dose which always kills the animal when injected intravenously, intramuscularly, or subcutaneously.[6] Our lethal dose for the dog is 480 guinea-pig LD50's per kilogram of dog's weight (see footnote 4 of Paper VII in Doctor Abel's[7] series); for cats and rabbits 960 guinea-pig LD50's per kilo; and for monkeys four guinea-pig LD50's per kilo.

Concentrated* tetanus toxin was supplied by Doctor Hampil of Sharp and Dohme, Inc., and by Doctor Malcolm of the Lederle Laboratories. The toxin was kept in sterile rubber-stoppered vials at 2° to 4° C. The strength of the toxin was frequently assayed on guinea-pigs. For further details regarding the preparation of the toxins and methods of assay the reader is referred to Section II of Paper V in Doctor Abel's[8] series. Doctor Brewer of Hynson, Westcott, and Dunning performed sterility tests on the toxins.

Large amounts of concentrated tetanus antitoxin were supplied by Sharp and Dohme, Inc.

Our injecting syringe has been described earlier.[5] With this syringe we can inject accurately as little as 0.0005 cc. of fluid.

TRTM.—In our tables we use this abbreviation for tactile reflex motor tetanus, by which we mean that the reflex activity of that part of the spinal cord which has been injected with toxin is so greatly exaggerated that in the *advanced* stage of this condition there are almost continuous extensor convulsions without any of the other symptoms of tetanus. Since in most of our experiments we injected the lumbar cord, the reflex motor tetanus was limited to the muscles of the hind limbs with the occasional involvement of some of the lower trunk muscles. The first sign to appear is hyperactivity of the deep reflexes. Later, testing the deep reflexes may produce a slight extensor clonus. If the animal is standing on all fours a pat on the lower end of the spine will cause the animal to extend his hind legs so sharply that his rump appears to bounce up. A little later the mere pressure of the animal's own weight when standing is sufficient to produce series of rapid extensor thrusts so that the hind legs appear to be dancing. Shortly thereafter the slightest tactile stimulus is enough to initiate exaggerated extensor thrusts. The symptoms are described in more detail by Firor and Jonas[3] in their protocols and by ourselves.[5]

Onset of Symptoms.—One column in the tables indicates the length of time between injection of toxin and onset of symptoms. It should be noted, however, that the animals were, in many instances, not examined frequently enough to detect the beginning of symptoms, and that, therefore, the number of hours in this particular column is not an accurate measure of the time required for the appearance of symptoms.

(I) *Infection of Toxin Into the Central Nervous System.*—EXPERIMENT I (*cf.* Expt. 2 in our previous report): To show that the injection of less than one lethal dose of tetanus toxin into an anterior horn of the lumbar cord can cause death, we have frequently repeated the operation used in 1937 by Firor and Jonas[3] and also described by us.[5] This procedure makes it possible to deposit the toxin in the anterior horn area with more accuracy than any other method we have tried. Counting all dogs, regardless of the size of the doses of toxin, a total of 196 dogs have been injected in the intact lumbar cord. For the sake of brevity these dogs are hereafter usually referred to as "intact cord dogs." One hundred dogs received less than one lethal dose; 46 dogs received more than one lethal dose; 23 dogs sacrificed for other experiments and not included; 27 dogs used in antitoxin experiments described later. The results of the operations on the first group of 100 dogs are given in Table IA.

* Our toxins varied in strength from 50,000 to 375,000 guinea-pig LD50's per cubic centimeter. It would require only 0.0007 cc. of our strongest toxin to kill a man weighing 154 pounds.

TABLE I A

INJECTION OF LESS THAN ONE LETHAL DOSE OF TETANUS TOXIN INTO THE INTACT LUMBAR CORD

All Autopsies Normal Unless Otherwise Noted

A. DOGS

Fraction of Lethal Dose Injected	Number of Animals	Onset of Symptoms in Hours	Symptoms	Survival in Days: Range	Survival in Days: Average	Autopsy and Remarks
1/2000	1		None	Indefinite		
1/1000	4		One had slightly increased reflex excitability	Indefinite		
1/500	1	48	Marked TRMT.	4 days *		
	1	120	Mild TRMT. which disappeared	Indefinite		
	1		Questionable increase in reflexes	Indefinite		
	4		No symptoms	Indefinite		Reinjected †
1/400	2	80	Marked TRMT.	9 days 12 days		Infection of cord
	5	100	TRMT. which disappeared	Indefinite		Four reinjected
	1	94	Atypical TRMT.	9 days		
	4		Questionable increase in reflexes	Indefinite		Two reinjected
	1		No symptoms	Indefinite		Reinjected
1/300	1		Questionable increase in reflexes which disappeared	Indefinite		
1/250	2	96	TRMT. which disappeared	Indefinite		
1/200	3	50	TRMT.	3–7	4.4	
	2	100	TRMT. which disappeared	Indefinite		
1/100	2	48	TRMT.	5–7	6	
1/50	5	48	TRMT.	3–7	4.6	
1/25–1/15	17	40	TRMT.	1–3	2.4	
	1	96	TRMT. and stiffness	6		Cord injured at operation
	3		No symptoms ‡	2–17	8	Had pneumonia
	3		No symptoms ‡	Indefinite		Reinjected
	1		No symptoms ‡	4		Normal
				Survival in Hours		
1/10	10	20–30	TRMT.	30–44	42	
	2	42	TRMT.	86		
1/8–1/3	11	20	TRMT.	24–60	33	
	1	72	TRMT. and stiffness	144		Cord injured at operation
1/2	11	15–17	TRMT.	18–53	38	

TABLE I B

B. CATS

Fraction of Lethal Dose Injected	Number of Animals	Onset of Symptoms in Hours	Symptoms	Survival in Hours: Range	Survival in Hours: Average	Autopsy and Remarks
1/400	1	96	TRMT.	120		The following animals were also injected with similar results: 4 rabbits, 4 guinea-pigs, 2 monkeys
1/150	2	60	TRMT.	120		
1/80	1	48	TRMT.	60		
1/40–1/20	2	42	TRMT.	78		
1/10–1/2	3	22	TRMT.	24		

* In the case of this dog the toxin was roughly diluted to a strength suitable for the injection. He probably received more than 1/500. Subsequently our dilutions were made with considerable accuracy, and under nitrogen to avoid oxidation.

† A number of dogs were reinjected with varying doses of toxin. We have not performed enough of these experiments to justify any deductions in regard to the effect of repeated small doses of toxin in the cord.

‡ All seven dogs were experimented upon before we had perfected our operating and injecting technic.

Tables IA and B reveal that injection into the intact cord has several points of similarity to intravenous injections of toxin:

(1) An incubation period before the onset of symptoms the length of which in general varies inversely with the amount of toxin injected.

(2) A survival period the length of which in general varies inversely with the amount of toxin injected.*

(3) The possibility of injecting (a) so little toxin as to produce no symptoms, or (b) enough to produce symptoms from which the animal later entirely recovers, or (c) an amount that always causes death.

(4) Individual variations in sensitivity to the toxin.

The table also reveals that usually in any one group of animals the period of incubation and of survival is longer in some individuals than in most of the other animals in their group. We feel that in addition to individual variation in sensitivity to toxin we may explain these differences by presuming that in these dogs the point of the injecting needle was not entirely within the motor area. The two dogs that developed stiffness suffered trauma to the cord during the operation. We have found, as did Firor and Jonas, that trauma to the cord almost always causes stiffness and prolongation of life. This factor is discussed below under Experiment 4.

Whenever these animals were observed at the time of death it was noted that respirations became slow and irregular before ceasing, but that the heart continued to beat for a minute or two, and not infrequently for as long as five minutes, after respirations had stopped. There was no rigidity or spasm of any of the muscles concerned with respiration as is often reported in patients

* It follows from (1) and (2) that if an animal has received enough toxin to kill him, the sooner symptoms appear the sooner the animal dies.

with tetanus dying of respiratory failure. Other observations on these animals are given later in this paper in discussing possible explanations for their death.

We also injected less than a lethal dose of tetanus toxin into the lumbar cord of cats, rabbits, monkeys, and guinea-pigs (Table IB) in order to show that such injections cause limited tactile reflex motor tetanus and invariable death in animals other than dogs.* It is of interest to note that our cats did not have hyperpyrexia before death such as was almost always found in dogs dying as a result of these injections.

In Table IC we give the results of injecting into the intact cord more than one lethal dose. In Table ID we summarize our controls. The operations on the control animals were exactly similar to the operations on the experimental animals. The inclusion of the seven controls reported by Firor and Jonas[3] is permissible because the operations on these dogs were exactly similar to our operations.

TABLE IC

INJECTION OF MORE THAN ONE LETHAL DOSE OF TETANUS TOXIN INTO THE INTACT LUMBAR CORD

Number of Lethal Doses Injected	Number of Dogs	Onset of Symptoms in Hours	Symptoms	Survival in Hours		Survival in Days If the Toxin Had Been Injected *Per Venam**
				Range	Average	
1.5	37	10–12	TRMT.	11–50	20	6
3.0	7	6	TRMT.	10–19	17	5
5.0	2	6	TRMT.	9–12	10.5	5

* These figures are taken from a number of experiments performed by Doctor Abel and his coworkers and by ourselves.

TABLE ID

CONTROL OPERATIONS AND INJECTION OF OTHER MATERIALS

Materials Injected	Number of Dogs	Survival in Days		Remarks
		Range	Average	
Staphylococcus toxin, diphtheria toxin, water, broth, needle punctures	8	8–120	40	Sacrificed or given away
	2	10–15	12	Died of pneumonia
Beef extract or veal infusion broth	4	Indefinite		Reported by Firor and Jonas[3]
Boiled tetanus toxin	3	Indefinite		
Dogs in Table I that received small doses of tetanus toxin but lived indefinitely	29	Indefinite		

* Although our experiments on animals other than dogs are too small in number to allow any positive statements to be made in regard to them, we suspect that in order to produce death by injecting toxin into the spinal cord, relatively larger fractions of a lethal dose are required for animals that are very sensitive to the intravenous injection of toxin than for less sensitive animals. For further studies on this point see J. Immunol., 37, 425, 1939.

We also injected less than one lethal dose of tetanus toxin into levels of the spinal cord other than the lumbar enlargement with similar results. Just as injection of the lumbar cord causes tactile reflex motor tetanus limited to the hind limbs, so, for example, injection of the cord in the cervical segment (C. VI) produces tactile reflex motor tetanus limited to the forelegs. We have not studied the survival period after injection of toxin into sensory areas of the medulla spinalis or oblongata because such injections invariably produce tetanus dolorosus. We have noted, however, that symptoms develop at the same time as in the motor area injections; and we believe that the survival period would also be the same as in the motor area injections.

For various reasons, which we shall discuss later, we desired to inject tetanus toxin into the region of the respiratory centers of dogs.[9] EXPERIMENT 2 (*cf.* Expt. 4 in our previous report): Toxin was injected into the medulla oblongata at the obex in 61 dogs. For the sake of brevity these dogs are hereafter usually referred to as "medulla dogs." Sixteen of these were sacrificed for other experiments, and in 11 dogs the outcome was complicated by additional procedures or by other pathologic conditions, such as pneumonia. The remaining 34 dogs and the controls are presented in Table II.

It is apparent that almost all the comments made in reference to Table I apply equally to Table II. There are the same points of similarity to intravenous injections of toxin. In general the variations of survival in any one group of medulla dogs are less than in the intact cord dogs. This is probably due to the fact that in the medulla dogs there is little chance of inserting the needle so deeply as to pass entirely through the cord, and, therefore, there is more chance of depositing the whole dose within the neural substance.

The manner of death was the same as in the intact cord dogs: there were no spasms of the respiratory muscles that could have suffocated the dogs; the heart continued to beat after respirations had ceased. In a few animals picrotoxin was injected intravenously in an attempt to stimulate the respiratory center.[10] These attempts were futile.

At autopsy the dogs dying from injections of diphtheria toxin had gross and extensive areas of hemorrhagic necrosis about the site of injection; these areas were sometimes as large as 2 to 3 Mm. in diameter. Diphtheria toxin placed in the lumbar cord produces a similar hemorrhagic necrosis causing flaccid paralysis of the hind limbs but not death.

The dogs injected with morphine received from 0.20 to 1.07 mg. of morphine sulphate per kilogram of body weight. Our solutions of morphine were made up in distilled water and contained from 80 to 160 mg. per cc. Within 15 minutes after the injection the animals' respirations became depressed and there appeared signs of medullary irritation somewhat similar to those which develop in dogs which had received tetanus toxin in the medulla. It is interesting that the injection of morphine, a known respiratory depressant, into the medulla at the obex produces almost immediate slowing of the respirations.

It should be noted that the incubation period before the onset of symptoms is still present even though we inject into the medulla an amount of toxin 2,500 times greater than what we may call an "intramedullary lethal dose," and that there is still a considerable period between the onset of symptoms and the death of the animal.

There are three chief differences between the intact cord and the medulla dogs: (a) In the medulla dogs smaller doses of toxin suffice to cause death

TABLE II

INJECTIONS OF TETANUS TOXIN INTO MEDULLA OBLONGATA AT OBEX

All Autopsies Normal Unless Otherwise Stated

A. EXPERIMENTAL

Fraction of Lethal Dose Injected	Number of Dogs	Onset of Symptoms in Hours	Symptoms	Survival in Hours: Range	Survival in Hours: Average	Autopsy
1/4500	2		None	Indefinite		
1/2000	1	48	Pharyngeal spasms	144	192	Pneumonia
	1	168	Pharyngeal spasms	240		Thin
1/1000	1		None	Indefinite		
	1	144	Pharyngeal spasms	408		Lost 30% weight
	3	132	Pharyngeal spasms	144–216	184	
1/500	2	24–48	Pharyngeal spasms	72–216	144	
1/40	3	18–24	Pharyngeal spasms	27–60	43	
1/20	2	5	Pharyngeal spasms	22–24	23	
1/15	5	7	Pharyngeal spasms	18–27	22	
1/10	7	6	Pharyngeal spasms	17–26	21	
1/5	2	Not seen	Pharyngeal spasms	17–19	18	
2.5	2	2	Pharyngeal spasms	10–12	11	
3.0	2	2	Pharyngeal spasms	9–11	10	

B. CONTROL

Number of Dogs	Material Injected	Amount in Cc.	Symptoms	Survival in Hours: Range	Survival in Hours: Average
1	Diphtheria toxin	0.0005	None	312	
3	Diphtheria toxin	0.001	None	19–23	21
3	Diphtheria toxin	0.002	None	23–36	29
2	Diphtheria toxin	0.003	None	15–40	27
2	Diphtheria toxin	0.004	None	15–17	16
2	Diphtheria toxin	0.006	None	9–19	14
5	Diphtheria toxin	0.008	None	17–23	19
3	Diphtheria toxin	0.01	None	8–33	17
5	Other bacterial toxins*	0.005	None	Indefinite	
1	Blood	0.006	None	Indefinite	
2	Water	0.004	None	Indefinite	
6	Tetanus spores and lactic acid	0.005	None	Indefinite	
5	Morphine sulphate	0.016–0.030	Yes	Indefinite	
1	Needle punctures and hemorrhage		None	Indefinite	

* Colon, typhoid, Staphylococcus, and meningococcus toxins.

See also the dogs used by Gesell, Bricker, and Magee, in which sharp needles and electrodes were put into the medulla.

than in the intact cord dogs. (b) With equal doses symptoms appear earlier in the medulla group. (c) When given equal doses of toxin the medulla dogs die about twice as quickly as the intact cord dogs.

In 12 dogs we injected toxin into the brain. Two dogs received ¼ to ½ lethal dose in the vermis. They both developed typical signs of cerebellar dysfunction and died in two and eight days. Ten dogs received 1/25 to ½ lethal dose in the frontoparietal area. Of these, five dogs developed no symptoms and survived indefinitely. Five dogs developed symptoms of varying degree but only two dogs died, in two and nine days; the other three survived indefinitely. Apparently the injection of toxin into the brain is seldom fatal. It is interesting to recall that patients with tetanus exhibit few signs of cerebellar irritation. We hope to increase our series of injections into the brain and to discuss in a later paper the differences between injections into the brain and into the spinal cord.

(II) *Injection of Toxin Into Organs Other Than the Central Nervous System.*—To show that less than one lethal dose does not kill when injected into organs other than the central nervous system we have made injections into veins, liver, spleen, testis, the anterior chamber of the eye, the spinal fluid, and motor roots. All these dogs lived indefinitely and exhibited no symptoms. We may also add the 13 dogs injected in the sciatic nerve by Abel, Hampil, and Jonas.[11] Two dogs injected in a sympathetic ganglion showed pupillary changes but they survived indefinitely. Dr. A. M. Harvey has written (1938) that he has had similar results with five dogs.

Since a small fraction of a lethal dose of tetanus toxin placed in the nonvital lumbar cord invariably kills the animal, and since such minute amounts of toxin put into any organ other than the central nervous system fail to kill the animal, we must find some explanation for the deaths.

(III) *The Factor of Muscular Contractions.*—Experiment 3 (*cf.* Expt. 1 in our previous report): To show that exhaustion of abnormal metabolites produced by the constant clonic seizures is not responsible for death, we severed the conus and two to three pairs of adjacent spinal roots and then immediately injected toxin into the mobilized end of the cord a centimeter or two proximal to the site of transection. For the sake of brevity these dogs are hereafter usually referred to as "caudal dogs." The animals of course had no convulsions. The results of these operations are given in Table III.

A comparison of uniform groups of dogs in Tables I and III receiving the same dose of toxin reveals that on the whole the caudal dogs in Table III lived longer than the intact cord dogs in Table I.

	Survival in Hours	
Dosage	Caudal Dogs	Intact Cord Dogs
1/90–1/50	72	120
1/50–1/2	77	49
1.5 –2	53	20

This difference is, we believe, probably due to trauma, a factor which we shall discuss under Experiment 4, and to interference with the blood supply

to the injected area. Even without Experiment 3 we should feel that the constant clonic muscle spasms cannot be an important factor in causing death because a dog that receives into the intact cord ¼ LD has convulsions for a matter of hours only while a dog receiving 1/100 LD or less may have just as violent convulsions for several days before he dies.

TABLE III

CAUDAL PREPARATIONS

All Animals After Operation Had Flaccid Paralysis of the Hind Legs; Six Dogs Injected with Tetanus Toxin Exhibited at Times Some Slight Jerking Movements of the Muscles of the Lower Trunk

A. EXPERIMENTAL

Fraction of Lethal Dose Injected	Number of Dogs	Survival in Days		Autopsy and Remarks
		Range	Average	
1/90–1/50	2	3		Normal
1/50–1/20	11	1–7	3.3	One dog had some cystitis
1/20–1/10	11	2–8	3.5	One dog had pneumonia One dog had an extensive subcutaneous infection around the incision
1/10–1/2	8	1–8	2.7	Normal
1.5–2	3	2–3	2.2	Normal
1/40–1/5	8	12–60	23	We feel that in these dogs the point of the needle was between nerve bundles rather than actually inside the cord. *Three of these dogs were re-injected and died within 2–4 days*

B. CONTROLS

Operation but no injection	4	5–51	23	The animal that lived 51 days died of urinary obstruction
Boiled toxin	4	5–20	13	One sacrificed Three died of pneumonia
Tetanus toxin	8	12–60	23	The animals listed on the last line of the first part (A) of this table may be considered as controls for the operation

(IV) *The Lethal Agent Is Not Transported Up the Spinal Cord.*—Could it be possible that the tetanus toxin travels from its point of injection in the lumbar cord up the spinal cord to a vital center? We determined to investigate this possibility, although (a) if unchanged toxin travels up the cord one would expect to see evidence (tactile reflex motor tetanus) of its passage and in not one of our dogs has such, or any, evidence presented that toxin, changed or unchanged, has traveled up the cord, and (b) in the absence of true lymphatics in the cord there is no known mechanism* by which toxin

* Toxin injected into the cerebrospinal fluid acts like toxin injected into the blood stream. To rule out the remote possibility that the toxin could travel up the central canal of the cord we tightly ligated the cord outside the dura and injected toxin distal to the point of ligation. Dogs prepared in this manner behaved in every respect like the dogs in Table IVA.

could so travel within the time limits of our experiments, and (c) even those who still adhere to the nerve transport theory* of tetanus, if we understand them correctly, no longer believe that the toxin can travel up within the substance of the cord. Ignoring these arguments, however, we carried out EXPERIMENT 4 (*cf.* Expt. 3 in our previous report) : To rule out the possibility that the toxin travels from its point of injection up the spinal cord to any vital center, we injected less than one lethal dose of tetanus toxin into the motor area of the distal segment of a transected cord. For the sake of brevity these dogs are hereafter usually referred to as "transected cord dogs." These operations are summarized in Table IVA, and the operations on the controls in Table IVD.

It is apparent that, on the whole, these dogs react to the injection of toxin similarly to those in Table I in spite of the fact that the toxin was injected into a cord the physiology of which had been severely altered by transection. Although in Table IVA we have included all dogs in which the injection may not have been entirely within the substance of the cord and have omitted any animals that had any pathologic condition† (in lungs, and so on) which might have hastened death, while in Table IVD (controls) we have included such animals, the average survival of the experimental animals was less than 10 days, of the controls was more than 33 days. It is obvious that the toxin, changed or unchanged, could not have reached the vital centers by traveling up the cord because the cord was not only divided but in almost every dog a piece of cord was excised so that it was quite impossible for the cut ends to come together.

It is interesting to note that in the transected cord dogs the interval between injection and onset of symptoms is approximately the same as in the intact cord dogs.

There are two chief differences between the transected and the intact cord dogs: (a) The transected cord dogs live several (3 to 7) times as long as the intact cord dogs ; and (b) some stiffness of the hind limbs is often superimposed on the tactile reflex motor tetanus. These two differences have been observed previously.[3] We have frequently observed in our intact cord injections that if the cord is injured (for example, by the rongeur's slipping and bruising the cord) stiffness appears in the affected limbs and life is prolonged for almost as long as if the cord had been transected. We feel that the stiffness is probably due to the injury of the transection, and that the transection so alters the physiology of the cut cord as to prevent the prompt utilization of the toxin, with the result that life is prolonged.

This stiffness of the hind limbs did not appear in all dogs, was very mild in most of the dogs, and in only one or two dogs approached that degree of unyielding rigidity found in local tetanus in which the muscles of the limb are directly injected with toxin. This

* The idea that the toxin is altered is in no way dependent, as will be seen, on any particular theory regarding the route by which the toxin reaches the vital centers.

† In many dogs, experimental and control, the urine at autopsy was very dark and in a few cases obviously bloody.

stiffness could always be abolished temporarily by anesthetizing the animal with ether provided the stiffness had not persisted for so long that permanent contractures had developed. As an explanation of this stiffness it has been suggested that in some way the tetanus toxin enables the cord to recover very rapidly from the period of so-called neural shock after transection, and that the stiffness may be simply ordinary spastic paralysis after transection. All of our control animals, with two or three exceptions, had persistent flaccid paralysis of the hind limbs. Of course, when the toxin is injected proximal to the point of section (see Table IVB) there is no stiffness.

TABLE IV

INJECTION OF TETANUS TOXIN INTO THE TRANSECTED LUMBAR CORD

A. FIRST: CORD TRANSECTED. LATER: TOXIN INJECTED DISTAL TO SECTION

All Dogs Had TRMT. and Normal Autopsies Unless Otherwise Noted

Number of Dogs	Transection at	Interval in Hours	Injection at	Fraction of Lethal Dose Injected	Onset of Symptoms in Hours	Survival in Days: Range	Survival in Days: Average	Remarks
1	D. VI	168	L. II	1/2	72	22		
3	D. XI	144	L. II	1/3–1/6	24–48	5–12	8	
2	D. XI	120	L. II	1/5	24–48	12–14	13	
1	D. XI	96	L. II	1/3	24–48	7		
1	D. XI	96	L. VI	1/3	72	16		Injection into conus
2	D. V	72	L. III	1/20	24	5– 9	7	
4	D. VII	0.3	L. II	1/2	24	2–11	6	

B. FIRST: CORD TRANSECTED. LATER: TOXIN INJECTED PROXIMAL TO SECTION

1	L. III	0.7	C. VII	1/8	36	3		TRMT. of forelimbs

C. FIRST: TOXIN INJECTED. LATER: CORD TRANSECTED PROXIMAL TO INJECTION

All Dogs Had TRMT. and Normal Autopsies Unless Otherwise Noted

Number of Dogs	Injection at	Fraction of Lethal Dose Injected	Interval in Hours	Transection at	Onset of Symptoms in Hours	Survival in Days: Range	Survival in Days: Average	Remarks
3	L. II	1/2	6	D. VI	40	2– 6	4	
2	L. IV	1/18	5	D. VI	None	10–30	20	No symptoms
1	L. IV	1/18	4	D. VI	24	5.5		
1	L. II	1/18	3.5	D. VI	96	19		

D. CONTROL OPERATIONS

All Dogs Had Flaccid Paralysis

Number of Dogs	Transection at	Interval in Hours	Injection at	Material Injected	Survival in Days: Range	Survival in Days: Average	Autopsy and Remarks
2	D. VI	0.3	L. II	Needle puncture	28–81	54	Loss of weight
1	D. VI	168	L. II	Needle puncture	10		

TABLE IV (*Continued*)

Number of Dogs	Transection at	Interval in Hours	Injection at	Material Injected	Survival in Days: Range	Survival in Days: Average	Autopsy and Remarks
1	D. VI	0.7	L. IV	Boiled toxin	29		
5	D. VI–IX	No second operation			30–90	61	
2	D. IX–XI	No second operation			1– 4	2	Bloody fluid in peritoneal cavity. Bladder distended and full of dark, bloody fluid
2	L. V	No second operation			5– 8	6.5	One had extensive infection and was sacrificed in 8 days. One had priapism, greatly distended bladder with hemorrhagic cystitis, hydro-ureters, *etc.*
4	D. VI and LV	No second operation			5–50	20	
2	L. II	No second operation			14–70	42	

Further confirmation of Experiment 4 is found in one dog into whose intact lumbar cord we injected 2,000 guinea-pig LD50's of tetanus toxin. Twenty-four hours later when the dog had marked tactile reflex motor tetanus and was almost dead the entire dorsal cord was removed and implanted through a hollow needle under the skin of the right thigh of one guinea-pig. The guinea-pig subsequently developed a slight stiffness of the right hind leg which disappeared in about two weeks, thus demonstrating that in this length (5 cm.) of cord there was not even one guinea-pig lethal dose.

In a few dogs toxin was injected into an isolated segment of cord, *i.e.*, the cord was cut above and below the point of injection. The only difference observable between these dogs and those in Table IVA were: (a) There was no stiffness in any dog; and (b) fewer muscles were involved in the clonic movements, especially if the two points of section were close to the point of injection.

(V) *The Toxin Molecule Is Not Multiplied.*—If the toxin molecule is multiplied within the lumbar cord and remains there, death would not ensue because the lumbar cord is not a vital center. Apparently some toxin does remain for many hours at the site of injection because we have excised the injected area 19 to 24 hours after injection and put the toxiferous cord into the intact cords of normal dogs; and although some of these recipient dogs developed mild tactile reflex motor tetanus, none died. These dogs should have died if the toxin were multiplied to any significant degree and remained at the site of injection.

If the toxin molecule is multiplied within the lumbar cord it must be removed from the cord in order to reach a vital center. We have demonstrated in Experiment 4 that toxin, whether multiplied or not, whether changed or unchanged, does not travel along the spinal cord or in the cerebrospinal fluid in reaching its site of lethal action. Therefore, if the toxin is multiplied it must be removed by the blood and lymphatic systems and distributed throughout the body. If amounts sufficient to cause death are so distributed one would

expect to see such signs of general tetanus as muscle rigidity, opisthotonos, and trismus. These signs never appear after the injection of toxin into the cord (*cf.* Expt. 5 in our previous report). We have assayed the blood of animals dying from injection of toxin into the cord. No toxin was demonstrable in the blood. We have also injected tetanus antitoxin intravenously into such dogs before the injection of the toxin into the cord and at varying intervals thereafter. If death were due to a multiplication of the toxin molecule as such, one would expect this antitoxin to be used up or destroyed.* But assays fail to show such use or destruction. There is no decrease in the circulating antitoxin in amounts greater than can be accounted for by the limit of error of our assay. Furthermore, assays show that dogs may die with large amounts of free antitoxin circulating in the blood and lymphatic systems (see Experiments 5 and 6 below).

Dr. R. B. Hyde very kindly tested on chicken embryos the possibility that toxin alone or toxin-bearing areas of cord produce a transmissible virus effect. These experiments were negative.

Since we have shown that (a) the principal factor causing death is not the metabolic changes consequent to the constant muscular spasms; and that (b) the blood and lymphatic systems are the only remaining pathways by which the lethal agent can reach a vital center; and that (c) the tetanus toxin itself is not multiplied, it seems permissible to suggest that tetanus toxin in the spinal cord is changed into a new lethal agent that is absorbed by the blood stream and carried to some vital center.

(VI) *The Effect of Tetanus Antitoxin.*—Abel and Chalian[12] showed that after the intravenous injection of one or more lethal doses of tetanus toxin, the administration of even large amounts of antitetanic serum fails to save life if before the serum is given the animal has clearly evident symptoms of a descending tetanus and has fixed in his tissues one or more lethal doses of the toxin. They showed further that even though the animal's tissues had fixed many lethal doses of the toxin, the antitetanic serum could save life if given not later than at a certain stage of the incubation period before the appearance of symptoms of general tetanus. We thought it would be interesting to study the effect of antitoxin on tactile reflex motor tetanus. EXPERIMENTS 5 and 6: Our injections of tetanus toxin into the lumbar cord and into the medulla were made as usual. The dogs received their antitoxin *per venam*. In Table V we give the results of injecting antitoxin before and after the injection of toxin into the intact lumbar cord, in Table VI the results of injecting antitoxin before and after the injection of toxin into the medulla.

We have expressed the amount of tetanus antitoxin as so many "neutralizing doses of TAT." By one neutralizing dose of antitoxin we mean that amount of antitoxin which is just enough to protect the animal (i.e., prevent death) against a given amount of toxin when both are injected *per venam*, the toxin immediately after the antitoxin. In such experiments one American unit of antitoxin per kilogram will prevent death in an animal which receives 6500 guinea-pig LD 50's of toxin per kilogram. Hence in the tables each "neutralizing dose" represents one unit of antitoxin for each 6500 guinea pig LD 50's of

* See Experiments 5 and 6 for a note on the absence of any blood-brain barrier for tetanus antitoxin.

toxin or for each 13.5 dog lethal dose. When we say we gave 100 or 500 neutralizing doses of antitoxin we mean that we injected 100 to 500 times as much antitoxin as would have been necessary to protect against the toxin injected had both been given intravenously, the toxin immediately after the antitoxin.

In a subsequent paper we shall deal more extensively with the protecting value of antitoxin against toxin introduced by various routes. We shall demonstrate that although the protecting value is less when the toxin is introduced intramuscularly, subcutaneously, or intracutaneously than when toxin is given intravenously, the only route by which the difference is really remarkable is when the toxin is injected directly into the lumbar cord or medulla.

TABLE V

TETANUS TOXIN IN INTACT LUMBAR CORD, TETANUS ANTITOXIN INTRAVENOUSLY

All Autopsies Normal

A. ANTITOXIN BEFORE TOXIN

Dog Number	Fraction of Lethal Dose Injected	Neutralizing Doses of Antitoxin	Interval in Hours Between Injection of TAT. and of Toxin	Symptoms Before Injection of TAT.	Symptoms After TAT.	Survival in Days	Remarks
437	1/2	800	0.5		Yes	2–	No prolongation of life
560	1/2	1,600	0.5		Yes	4	Life prolonged
438	1/2	4,000	0.5		No	Indefinite	Completely protected
439	1/2	8,000	0.5		No	Indefinite	

All Autopsies Normal

B. TOXIN BEFORE ANTITOXIN

81	1/12	2,400	0.5	No	Yes	2–	No prolongation of life
80	1/12	5,600	0.5	No	Yes	8	Life may be prolonged, but usually is not prolonged
403	5.0	400	3.0	No	Yes	1	
440	1/2	800	6.0	No	Yes	5	
655	1/2	800	6.0	No	Yes	2.2	
443	1/2	4,000	6.0	No	Yes	1	
442	1/2	8,000	6.0	No	No	Indefinite	Symptoms may appear, but life is spared
441	1/2	40,000	6.0	No	Yes	Indefinite	
410	3.0	560	10.5	Yes	Yes	1–	No protection
411	3.0	800	10.5	Yes	Yes	1–	
594	1.5	1,000,000	13.5	Yes	Yes	1–	
675	1/20	8,000,000	115.0	Yes	Yes	5.8	

If we assume that the lethal dose for intact cord and for medulla injection is 1/100 and 1/500 of the intravenous lethal dose, it is apparent that, in general, our results parallel those of Abel and Chalian[12] in whose experiments the toxin was injected intravenously. After the appearance of definite symptoms even relatively enormous doses of antitoxin do not affect the outcome. The longer the interval before the injection of antitoxin, the larger must be the amount of antitoxin given in order to prolong or to save life.

A very striking feature of these experiments is that even when the anti-

toxin is given *before* the toxin, relatively large amounts of antitoxin are required to save life or even to prevent the appearance of symptoms, and this is especially true when the toxin is injected into the medulla. Some readers may resurrect the theory that there is a barrier which prevents the antitoxin in the blood from reaching the toxin in the cord. But obviously no such barrier exists, because if sufficiently large doses of antitoxin are given before the onset of symptoms the animals develop no symptoms and do not die. The antitoxin must, therefore, have migrated from the blood to the substance of the cord.* It may be that the concentration of antitoxin brought by the blood to the injected area is too small to neutralize quickly the admittedly high concentration of toxin injected directly.

TABLE VI

TETANUS TOXIN IN MEDULLA, TETANUS ANTITOXIN INTRAVENOUSLY

All Dogs Received 1/10 Lethal Dose of Toxin. Autopsies Normal Unless Noted

A. ANTITOXIN BEFORE TOXIN

No. of Dogs	Neutralizing Doses of Antitoxin	Interval in Hours Between Injections of TAT. and of Toxin	Symptoms Before Injection of TAT.	Symptoms After TAT.	Survival in Days	Remarks
14	8–8,000	0.25–0.5		Yes	1.6	No prolongation of life
1	10,000	0.25–0.5		Yes	4.0	Symptoms present. Life prolonged
2	16,000	0.25–0.5		Yes	4.3	
1	32,000	0.25–0.5		Yes	6.0	
2	40,000	0.25–0.5		Yes	12.0	
1	64,000	0.25–0.5		No	Indefinite	Mild symptoms generally appear but life is usually saved
1	80,000	0.25–0.5		Yes	Indefinite	
1	92,000	0.25–0.5		Yes	20.0	
2	160,000	0.25–0.5		Yes	Indefinite	
1	400,000	0.25–0.5		No	Indefinite	Completely protected
1	800,000	0.25–0.5		No	Indefinite	

B. TOXIN BEFORE ANTITOXIN

1	400,000	6.0	No	Yes	2–	No prolongation of life
1	800,000	5.0	No	Yes	Indefinite	Symptoms may appear but life is spared
1	400,000	18.0	Yes	Yes	1.7	No protection
1	800,000	18.0	Yes	Yes	1.7	

There is the added factor of fixation of the toxin. Although no one knows what happens to tetanus toxin when it undergoes that change which is generally termed "fixation" (*i.e.*, the toxin can no longer be recovered in a form recognizable by our present methods of assay), it appears likely from the work of Abel and Chalian, although they do not say so, that there are two stages of fixation: (a) The fixed toxin can still be rendered innocuous by excessive amounts of antitoxin; and (b) the fixed toxin can no longer be neutralized by antitoxin although at this time the toxin may not yet have begun to cause recognizable symptoms but will inevitably do so. It may be that the neurones

* For further remarks on the absence of a blood-brain barrier see the papers by Doctor Abel and his coworkers, especially Paper VIII in his series.[12]

into which we inject the toxin fix the toxin so rapidly into stage (b) that the antitoxin has no chance to neutralize it. However, Experiment 6A seems to indicate: (1) That, on the contrary, the neurones, although exposed to a high concentration of toxin, fix it into stage (b) no more rapidly than when toxin is injected intravenously; and (2) that by intravenous injection antitoxin, unless in very large amounts, is not brought in sufficient concentration to the point of deposit of the toxin to neutralize the toxin. In the present state of our ignorance it is futile to speculate further upon the question of whether or not and how the toxin may be fixed.

The important fact is that, regardless of how the toxin may be fixed, it is necessary to administer large doses of antitoxin before the onset of symptoms, or earlier, if the animal is to be saved. That this holds true, even when the antitoxin is injected directly into the cord, is shown by Experiment 6A, in which toxin was injected into the medulla and at varying intervals thereafter antitoxin was injected into the same spot, as nearly as we could judge, into which the toxin had been injected.*

TABLE VI A

TETANUS TOXIN IN MEDULLA, TETANUS ANTITOXIN IN MEDULLA LATER

Dog Number	Fraction of Lethal Dose Injected	Interval in Hours Between Injection of Toxin and of TAT.	Neutralizing Doses of Antitoxin	Symptoms Before Injection of TAT.	Symptoms After Injection of TAT.	Survival in Days	Remarks
362	1/25	5.5	800	No	No	Indefinite	Completely protected
363	1/25	5.5	800	No	No	Indefinite	
365	1/25	11	800	Questionable	Yes	6.5	Life is prolonged
366	1/40	20	1,600	Questionable	Yes	5.0	
364	1/25	11	800	Yes	Yes	2.0	No protection
367	1/40	17.5	1,600	Yes	Yes	2.4	
356	1/10	18	3,200	Yes	Yes	1.5	
357	1/10	18	3,200	Yes	Yes	1.5	

Unfortunately, the doses of toxin used here were not the same as those injected into the dogs of Table VI; and, consequently, we cannot directly contrast the two entire groups of animals. It is obvious that once symptoms appeared no lives were saved by antitoxin; but we did not, in these dogs, use very large amounts of antitoxin for fear that too much fluid injected into the medulla would, by its bulk, cause disturbances leading to death.

It is apparent, however, that the intravenous injection of the antitetanic serum is far less efficient than the method of administering the antitoxin used in Experiment 6A; with the latter method 800 neutralizing doses given five hours after the injection of toxin are sufficient to confer full protection; with the former method, in order even to approximate the same degree of protection, 800,000 neutralizing doses of antitoxin must be given, if administered five

* This experiment was suggested and carried out by Dr. George G. Hogeboom.

hours after the injection of toxin; or 64,000 neutralizing doses if given *before* the injection of toxin.

(VII) *Excision of Cord Injected With Tetanus Toxin.*—In going over our records we noticed that once or twice when we had excised an injected cord for transplantation into another dog we did not, as was our usual practice, sacrifice the dog from which the cord had been taken. Our technician had recorded that these dogs continued to show tactile reflex motor tetanus and died fairly soon.

EXPERIMENT 7.—As this seemed unlikely, and as the removal of the injected area was another way of doing what we had tried to do in our antitoxin experiments (*i.e.*, prevent death), we injected toxin into the intact lumbar cord and, at varying intervals thereafter, we excised the injected area. The needle puncture was identified and the proximal level of section, ascertained by measuring the shrunken cord after excision, was always at least 1 cm. above the puncture and in every case we removed at least 2 cm. of cord. Our results are given in Table VII.

TABLE VII

EXCISION OF INJECTED AREA OF LUMBAR CORD

Number of Dogs	Site of Injection	Fraction of Lethal Dose Injected	Onset of Symptoms in Hours	Symptoms Present Before Excision	Interval in Hours Between Injection and Excision	Length of Cord Excised in Cm.	Symptoms Present After Excision	Survival in Days	
								Range	Average
2	L. I	1/40	48	TRMT.	48	?	TRMT.	2–10	7
1	L. II	1/10		None	19	?	Flaccid	11	
1	L. II	1/10		None	22	9.0	Flaccid	21*	
4	L. II	1/10	44	TRMT.	48	9.0	Flaccid	5–11	7.5
1	L. II	1/10	20	TRMT.	Control—cord not excised			1.5	
1	L. II	1/2		None	29	2.6	? Reflexes hyperactive	37	
2	L. II	1/2	24	Mild TRMT.	25	1.6	TRMT.	4–5+	5
1	L. II	1/2	24	TRMT.	47	1.8	TRMT.	3.6	
1	L. II	1/2	16	TRMT.	18	?	TRMT.	1.6	
1	L. II	1/2	16	Mild TRMT.	18	?	TRMT.	2.6	
2	L. II	Control—no toxin			28	1.7	Flaccid	14–70*	42

* Sacrificed.

We find if we excise only a small area of cord, that here again we must act before symptoms appear in order to save or to prolong life. If we act after the appearance of symptoms the animals usually continue to jerk and die sooner than the uninjected operative controls. If we excise a large area of cord after the onset of symptoms, life is prolonged and there are no symptoms after the excision of the cord.

(VIII) *Cross-Circulation Experiments.*—When the possibility of the alteration of tetanus toxin first occurred to us, we tried to demonstrate such alteration in a positive manner by injecting various amounts of toxin into the cord of dogs and then removing the toxiferous area and injecting that into the thigh muscles, peritoneal cavity, cord, or medulla of normal dogs in the hope that the normal dogs would die. We ignored the probability that the blood stream would remove any lethal agent in the cord of the donor dog and the possibility that, in the process of transferring the injected area from donor to recipient, exposure to air might destroy any lethal agent by oxidation. Of 63 dogs receiving such "transplants," 57 lived more than six days. Of the six dogs dying in less than six days, only two or three had no pathologic condition to account for death. We also tried incubating toxiferous cord *in vitro*. Here there was less chance of oxidizing a lethal agent, but on the other hand the cord was dead. These unnatural experiments also were negative.

As it became increasingly probable, however, that the results of our cord injections could be explained only on the basis (a) that the tetanus toxin is gradually altered; and (b) that the altered substance is not stored in the cord but (c) is taken up by the blood stream as it is formed, we cast about for another method of demonstrating such alteration. If the blood stream carries to the vital centers an altered lethal product of tetanus toxin, by transferring the blood of the affected dog into a normal dog it should be possible to kill the normal dog by means of this lethal agent, provided that there is enough of the lethal agent in the blood stream of the affected dog to kill both this dog and the normal dog. The most thorough and physiologic method of so transferring the blood is to unite the circulations of the two dogs, a procedure which we[13] had often performed previously in this laboratory, which we knew to be quite harmless although continued for several days, and which ensured a thorough intermingling of all the elements in the blood of the two dogs.*

EXPERIMENT 8.—The cross-circulation of normal dogs with dogs dying as a result of the injection of tetanus toxin into the medulla spinalis or oblongata or into the blood stream.

We employed our usual technic in injecting tetanus or diphtheria toxin into the lumbar cord, into the medulla, or into the veins of what we called the "donor dogs"; *i.e.*, they manufacture and donate the altered toxic agent to the normal or "recipient dogs." At varying intervals after the injection of toxin we united the circulations of the two dogs. A modified Carrel technic[13] was used to join by end-to-end anastomosis the common carotid artery of the donor dog to the external jugular vein of the recipient dog, and *vice versa*. At least 15 minutes before the anastomosis was opened, each recipient dog received enough tetanus antitoxin to neutralize many times the amount of tetanus toxin injected into the donor dog. The dogs were kept on the operating table throughout the experiment. The

* In a long continued cross-circulation experiment the blood streams of both animals will eventually have equal concentrations of the formed and chemical elements in the blood provided one animal is not receiving into its blood stream a steady supply of some element. But if, for example, one animal is receiving glucose solution *per venam* or is absorbing glucose from the stomach, the sugar content of his blood will remain persistently higher than that of the other animal not receiving such a supply. This should be kept in mind in reading the accounts of the following experiments.[14]

anastomoses and other exposed tissues were kept covered with cotton pads saturated with warm normal saline. The anastomoses were inspected every 30 minutes to make sure they were functioning properly. Very rarely a small clot would be found partially obstructing one anastomosis; these were promptly dislodged. The dogs operated upon under nembutal anesthesia were given additional small doses of nembutal whenever they became restless. Fluids were given, usually by mouth.

PROTOCOL OF TYPICAL EXPERIMENT

	Donor Dog No. 448: Tan, adult, female, 6.0 Kg.	*Recipient Dog No. 430:* Gray police puppy, 6 mos., female, 4.35 Kg.
October 24, 1938		
5:45 P.M.	Received 1.5 LD tetanus toxin into intact cord at L.II	
October 25, 1938		
9:30 P.M.	TRMT. T. 105.8°F.	
10:45	T. 106°F.	T. 101.6°F.
11:05	Received 0.16 Gm. nembutal intraperitoneally	Received 0.13 Gm. nembutal intraperitoneally
11:30	Cross-circulation operation begun. T. 104.6°F.	
12:00 Noon		Received 1 cc. TAT *per venam* (1,400 neutralizing doses)
12:35 P.M.	Anastomosis opened	
1:00	T. 104.2°F., P. 180, R. 20—Marked TRMT.	T. 102.3°F., P. 176, R. 20
2:00	T. 107.2°F., P. 240, R. 18—Restless	T. 104.6°F., P. 210, R. 28
2:20	Received 0.025 Gm. nembutal i.p.	
2:30	T. 108.4°F., P. 240, R. 140	T. 104.5°F., P. 200, R. 176
4:00	T. 109.8°F., P. 240, R. 80	T. 106.4°F., P. 240, R. 124
4:25	Respirations 88, irregular, and failing	R. 12
4:28	Anastomosis closed. Took sample of blood for hematocrit determination—42	Anastomosis closed. Took sample of blood for hematocrit—41
4:35	Respirations ceased	
4:37	Heart stopped	Respirations ceased
4:42	Autopsy normal	Heart stopped
		Autopsy normal. No evidence of blood loss or shock

Over 40 pairs of dogs were so cross-circulated. Tables VIII to XII summarize these operations. In Table VIIIA the cross-circulation was ended 2 to 30 hours before the death of the donor. Of the six recipients in Table VIIIA only one died. That even one dog died is surprising, because one could not expect the concentration of the altered substance to reach its maximum until fairly near the death of the donor dog. In the next series (Table VIIIB) we continued the cross-circulation until within a short time of death.

Of the 14 recipients in Table VIIIB, only two lived, a result which exceeded our expectations. We next sought to show that the mere fact of being cross-circulated with a dying dog would not suffice to kill the recipient. We killed donor dogs by a medullary necrosis consequent to the injection of diphtheria toxin into the medulla (Table IX).

TABLE VIII

CROSS-CIRCULATION. TETANUS TOXIN IN LUMBAR CORD OF DONOR DOG

Cross-Circulation Under Nembutal Anesthesia

A. CROSS-CIRCULATION ENDED 2 TO 30 HOURS BEFORE DEATH OF DONOR

Number of Donor Dog	Combined Weight in Kg. of Both Dogs	Lethal Doses of Tetanus Toxin Received by Donor	Neutralizing Doses of TAT. Received by Recipient	Interval in Hours Between Injection of Tetanus Toxin and Beginning of Cross-Circulation	Length in Hours of Period of Cross-Circulation	Total Nembutal Given in Grams	Period of Survival of Donor After Cross-Circulation Ended	Period of Survival of Recipient After Cross-Circulation Ended	Fate of Recipient	Remarks
337	15.7	0.5	5,600	4.5	7.0	0.93	30 hrs.		Lived	
378	11.2	5.0	800	6.7	1.5	0.36	4.2 hrs.		Lived	
388	12.4	0.3	9,600	25.5	5.5	0.43	6 hrs.		Lived	
399	9.4	0.5	4,000	23.0	16.0	0.80	13 hrs.	24 hrs.	Died	
402	12.8	5.0	400	3.5	11.0	0.60	14 hrs.		Lived	
426	8.6	1.5	1,000	15.3	6.0	0.40	2 hrs		Lived	

B. CROSS-CIRCULATION ENDED WITHIN 2 HOURS OF DONOR'S DEATH

371	12.1	0.05	56,000	49.0	8.3	0.52	0	0	Died	
391	12.2	0.5	6,000	18.5	27.0	0.84	0	7 mins.	Died	
417	7.5	1.5	1,400	14.0	4.0	0.33	1.5 hrs.	27 hrs.	Died	Recipient weighed 12 to 45% less than donor
418	13.2	1.5	880	15.5	5.0	0.48	2.5 mins.	30 mins.	Died	
447	10.1	1.5	1,440	17.0	7.5	0.38	4 mins.	2 mins.	Died*	
448	10.4	1.5	1,400	19.0	4.0	0.32	7 mins.	9 mins.	Died	
465	12.1	1.5	2,400	15.5	4.0	0.41	3 mins.		Lived	
605	25.2	1.5	368	13.0	4.3	0.75	3 mins.	18 hrs.	Died	
395	10.8	0.5	4,000	21.5	20.0	0.51	5 mins.	5.5 hrs.	Died	
398	14.1	0.5	3,200	21.0	5.0	0.56	10 mins.	0	Died*	Weights equal
424	9.9	1.5	1,400	14.2	5.3	0.35	2 mins.	2.5 hrs.	Died	
434	12.8	1.5	1,200	17.5	3.7	0.43	5 mins.		Lived	
433	6.8	1.5	2,480	13.5	5.0	0.20	8 mins.	4 mins.	Died*	Recipient weighed 20 to 35% more than donor
466	9.6	1.5	3,600	14.0	24.0	0.68	1 min.	6 mins.	Died	

* Dogs No. 447, 398, and 433: The recipient died before the donor.

TABLE IX

CROSS-CIRCULATION CONTROL. DIPHTHERIA TOXIN IN MEDULLA OF DONOR DOG

Cross-Circulation Under Nembutal Anesthesia

Number of Donor Dog	Combined Weight in Kg. of Both Dogs	Diphtheria Toxin in Cc. Received by Donor Dog	Interval in Hours Between Injection of Toxin and Beginning of Cross-Circulation	Length in Hours of Period of Cross-Circulation	Total Nembutal Given in Grams	Period of Survival of Donor Dog After Cross-Circulation Ended	Fate of Recipient
459	8.9	.008	17.5	0.5	0.2	0	Lived
517	11.5	.012	2.5	1.5	0.33	4 mins.	Lived
515	12.0	.008	2.0	21.2	1.6	5 mins.	Lived
520	12.9	.010	2.5	13.5	9.97	4 mins.	Lived
565	11.7	.011	2.0	8.5	0.70	0	Lived
567	12.2	.011	2.7	5.8	0.85	0	Lived

Since none of the recipients in Table IX died we felt that this procedure was an adequate control for the fact of death.

VARIOUS OTHER CONTROL PROCEDURES ON CROSS-CIRCULATED DOGS

(A) *Adequacy of Cross-Circulation:* In many dogs complete blood counts and hematocrit determinations were made during the course of the cross-circulation and after. The values for the donor and for the recipient were the same after the first five to ten minutes of cross-circulation.

(B) *Blood Pressure and Blood Volume:* In no case was there any pallor or other gross evidence of blood loss from one dog into the other. When both donor and recipient died within a few minutes of each other no gross differences could be detected in color or in filling of the vascular system. Dogs dying as the result of the injection of 1.5 lethal doses of toxin in the lumbar cord maintain normal blood pressure until about 20 to 30 minutes before death. At this time, the pressure falls gradually to 50 or 60 Mm. of mercury. During the last five minutes before death the pressure may fall to 20 Mm. Of course, after respiration ceases the pressure gradually drops to zero as the heart fails. Such a low pressure in the donor is not, in itself, sufficient to cause the death of the recipient, for the blood pressure falls similarly in dogs dying as the result of the injection of diphtheria toxin in the medulla oblongata without causing the recipients to die. During the cross-circulation of normal dogs[14] significant, but never fatal loss (25 to 30 per cent), of blood volume was suffered only by those dogs whose size and original blood volume were about twice as large as that of the dogs with which they were cross-circulated. The blood lost by the larger dogs caused a proportional increase in the blood volumes of the smaller dogs. This blood loss occurred in spite of the fact that the blood pressures of the larger dogs during the period of cross-circulation were only half as high as those of the smaller dogs. In our cross-circulation experiments with dogs that had received tetanus toxin in the lumbar cord or intravenously, 61 per cent of the donors weighed 10 to 50 per cent more than the recipients, 22 per cent were equal in weight, and in only 16 per cent did the donors weigh less than the recipients. In a majority of these experiments, therefore, if any blood were lost from one dog to the other it should have been lost by the donor to the recipient. To make sure that the recipient had plenty of blood we occasionally permitted the donor to pump blood into the recipient after the donor had stopped breathing. This procedure did not save the lives of the recipients.

(C) *Adequacy of Antitoxin:* Assays made of the antitoxin content of the blood of dying recipient dogs agreed with the known amount of antitoxin injected before cross-circulation. For example, one dog (No. 466) after 24 hours of cross-circulation still had 1.8 units of tetanus antitoxin in every cubic centimeter of serum.

(D) *Blood Chemistry:* Chemical studies on the blood revealed that the most persistent and striking change was a lowering of the blood sugar content. This change, however, appeared as often when the recipient lived as when he died. One recipient died with a blood sugar content of 93 mg. per cent. Four recipients died, although given large quantities of glucose by mouth and by vein during the period of cross-circulation.

We next cross-circulated dogs dying from an injection of tetanus toxin into the medulla oblongata (*cf.* Experiment 2).

None of the recipients in Table X died. This result made us wonder whether it could be possible that since the tetanus toxin is injected into or close by the respiratory center, its lethal agent does not have to be carried by the blood stream to a vital center, but rather the toxin is changed and has its lethal effect where it is injected, and death occurs before any large amount of the changed substance is present in the blood stream. We shall return to this point in the Discussion.

TABLE X

CROSS-CIRCULATION. TETANUS TOXIN IN MEDULLA OF DONOR DOG

Number of Donor Dog	Combined Weight in Kg. of Both Dogs	Lethal Doses of Tetanus Toxin Received by Donor	Neutralizing Doses of TAT. Received by Recipient	Interval in Hours Between Injection of Tetanus Toxin and Beginning of Cross-Circulation	Length in Hours of Period of Cross-Circulation	Total Nembutal Given in Grams	Period of Survival of Donor After Cross-Circulation Ended	Fate of Recipient
383	10.7	0.07	560	19.0	3.0	0.37	7 hrs.	Lived
576	10.6	3.0	400	2.0	1.5	0.37	0	Lived
589	10.5	2.5	320	2.0	10.0	Ether	0	Lived
580	13.3	2.5	376	3.2	7.0	Ether	0	Lived
584	14.2	3.0	360	2.5	9.1	Ether	0	Lived

It will be noted in Table X that in two instances the cross-circulation was carried out under nembutal anesthesia, and in three instances under ether anesthesia. In our previous cross-circulations we had always used nembutal because the position of the dogs' heads made it difficult to administer ether. In the case, however, of dogs that had, some hours earlier, received tetanus toxin in the medulla we found that the injection of our usual dose of nembutal in preparation for operation would very frequently be followed within 15 to 20 minutes by the death of the animal, whereas similar animals not receiving nembutal would live many hours longer; consequently we used ether as the anesthetic for the last three operations in Table X. But this unexpected complication made us wonder whether nembutal could be responsible for the death of the recipients in the earlier cross-circulation experiments. We, therefore, repeated the series in Table VIIIB, using ether for anesthesia instead of nembutal.

TABLE XI

CROSS-CIRCULATION. TETANUS TOXIN IN LUMBAR CORD OF DONOR DOG

Cross-Circulation Under Ether Anesthesia

Number of Donor Dog	Combined Weight in Kg. of Both Dogs	Lethal Doses of Tetanus Toxin Received by Donor	Neutralizing Doses of TAT. Received by Recipient	Interval in Hours Between Injection of Tetanus Toxin and Beginning of Cross-Circulation	Length in Hours of Period of Cross-Circulation	Period of Survival of Donor After Cross-Circulation Ended	Period of Survival of Recipient After Cross-Circulation Ended	Fate of Recipient	Remarks
592	13.3	1.5	368	14.0	4.9	0	10 mins.	Died	Recipient
593	12.1	1.5	368	12.0	7.0	1 min.		Lived	weighed 18 to
601	10.3	1.5	368	14.3	8.7	3 mins.		Lived	34 per cent less
623	11.5	1.5	368	14.5	6.5	1 min.	5 mins.	Died	than donor
600	14.9	1.5	368	13.0	5.7	2 mins.		Lived	Weights equal
609	14.0	1.5	736	13.0	4.3	3 mins.		Lived	Recipient weighed 24 to 53
610	16.5	1.5	736	14.2	12.8	3 mins.		Lived	per cent more than donor

Of the seven recipients in Table XI, only two died. This seemed to indicate that probably nembutal *had* played some part in the death of the earlier

recipients. But when we compared the amounts of nembutal received by recipients that died with the amounts received by recipients that lived, we could not find that the dying recipients received even as much nembutal as the recipients that lived.

Cross-Circulation With		Amount of Nembutal Received in Gm. Per Kilo Per Hour
Tetanus donor	13 recipients died*	0.0085 Gm.
Tetanus donor	7 recipients lived	0.0106 Gm.
Diphtheria donor	6 recipients lived	0.013 Gm.

* These 13 dogs died from 1.5 to 20 hours after receiving their last doses of nembutal. The average time was 7.3 hours; six dogs died in less than five hours, two of these in less than three hours.

It was obvious that the rôle, if any, played by nembutal in causing the death of the recipient was not a major one. It occurred to us that the depressive effect of nembutal on an already poisoned respiratory center might be sufficient to cause death when neither the nembutal nor the poison was present in sufficient amounts alone to cause death. This seemed to be a possible explanation of our results. To test this theory, Dr. Jonas Friedenwald suggested that we carry out our usual cross-circulation experiment under ether anesthesia and that we give a small and unquestionably safe dose of nembutal to the recipient immediately after cessation of the cross-circulation.

TABLE XII

CROSS-CIRCULATION. EFFECT ON RECIPIENT OF NEMBUTAL GIVEN AFTER CROSS-CIRCULATION ENDED

Cross-Circulation Operation Performed Under Ether Anesthesia

Number of Donor Dog	Combined Weight in Kg. of Both Dogs	Lethal Doses of Tetanus Toxin Received by Donor	Neutralizing Doses of TAT Received by Recipient	Interval in Hours Between Injection of Tetanus Toxin and Beginning of Cross-Circulation	Length in Hours of Period of Cross-Circulation	Total Nembutal Given in Grams	Period of Survival of Donor After Cross-Circulation Ended	Period of Survival of Recipient After Cross-Circulation Ended	Fate of Recipient	Remarks
A. TETANUS TOXIN IN LUMBAR CORD OF DONOR										
624	16.6	1.5	368	13.0	3.1	0.23	1 min.	15 mins.	Died	Usual dose of nembutal
B. TETANUS TOXIN IN VEIN OF DONOR										
672	14.5	100	288	40.0	2.7	0.11	0		Lived	Two-thirds of usual dose of nembutal
704	13.6	100	400	27.0	11.0	0.13	0	45 mins.	Died	"
705	10.2	100	480	25.0	12.4	0.11	0	1 hr.	Died	"

Of the four dogs in Table XII, only one survived, a result which tends to substantiate our explanation. In view of this and of the extensive clinical use of avertin and other hypnotics we thought it wise to examine the effect of nembutal and avertin on the course of general tetanus in dogs.

(IX) *The Effect of Hypnotics on the Survival of Dogs With Tetanus.*—EXPERIMENT 9.—Twenty-one dogs received *per venam* 1.5 dog lethal doses of tetanus toxin. As soon as the dogs showed such severe symptoms of general tetanus that they could no longer stand or eat, they were divided, in rotation, into three groups: Group A received repeated but nonlethal doses of avertin, sufficient in amount to stop convulsions for the course of the experiment. Group B received similar doses of nembutal. Group C received no treatment. Table XIII gives the results of this experiment.

TABLE XIII

THE EFFECT OF AVERTIN AND NEMBUTAL ON THE SURVIVAL OF DOGS WITH GENERAL TETANUS

All Dogs Received, Per Venam, 1.5 Lethal Doses of Tetanus Toxin

Hypnotic Used	Dog Number	Interval in Days Between Injection of Toxin and Onset of Severe Symptoms	Avertin or Nembutal in Grams per Cc. per Hour	Survival in Days After Onset of Severe Symptoms	Survival in Days After Injection of Toxin
AVERTIN	681	4.42	.044	1.88	6.30
	680	5.00	.043	1.88	6.90
	682	5.10	.054	1.19	6.29
	686	5.10	.040	1.94	7.04
	677	5.67	.100	0.43	6.10
	690	6.65	.020	2.92	9.57
	683	6.82	.212	0.04	6.86
	Average	5.54	.070	1.47	7.01
NEMBUTAL	697	3.66	.0050	1.64	5.30
	699	4.58	.0043	0.42	5.00
	692	5.07	.0025	3.10	8.17
	685	5.58	.0020	1.80	7.38
	700	5.58	.0040	3.70	9.28
	693	6.20	.0090	1.25	7.45
	Average	5.11	.0031	1.99	7.10
CONTROL	696	2.80	None	2.37	5.17
	689	4.00	"	3.50	7.50
	684	4.83	"	0.08	4.91
	687	5.00	"	3.12	8.12
	698	5.05	"	2.41	7.46
	695	5.07	"	4.33	9.40
	679	5.67	"	6.76	12.43
	694	7.63	"	4.54	12.17
	Average	5.01		3.39	8.41

It will be seen that the controls lived almost a day and a half longer than the dogs receiving avertin and nembutal, and that the controls, after they could no longer stand, lived almost two days longer than the dogs receiving avertin and almost one and a half days longer than the dogs receiving nembutal. If the abolition of convulsions has any effect in prolonging life it is obvious

that this effect should be more noticeable in the absence of any nourishment after the onset of severe symptoms. We conclude, therefore, that under the conditions of this experiment the administration of avertin or of nembutal is not only of no benefit but may actually be harmful.

The dose of avertin received by some of the animals was admittedly large, but on the other hand the dose of nembutal was known to be quite safe. For example, we have given, with no ill effects, to normal dogs doses of nembutal 33 per cent greater and for a 50 per cent longer period than the average of the experimental animals in Table XII. In Experiment 12, we were interested in giving enough of the hypnotic to stop convulsions and to confer some degree of relaxation. Although it is possible that in some instances the survival period of the dogs receiving avertin may have been shortened by toxic action of the avertin, it is obvious that the survival period was also shortened in those animals receiving doses of nembutal known to be harmless.

Discussion.—The injection of less than one lethal dose of tetanus toxin into a nonvital area of the central nervous system invariably kills dogs, cats, rabbits, guinea-pigs, and monkeys. As little as 1/400 of a lethal dose placed in the lumbar cord of a dog has produced symptoms and death. The injection of less than a lethal dose of toxin into organs other than the central nervous system is never fatal. This peculiar phenomenon calls for an explanation.

We have attempted to show that metabolic changes consequent to the constant muscular spasms are not the principal factor in causing death. In the absence of muscular spasms (Experiment 3) life is prolonged to some extent but death ensues fairly promptly. It seems likely that this prolongation of life is due to the impaired circulation of the cord and not to the abolition of convulsive movement. Furthermore, when toxin is injected into the intact cord, those animals receiving relatively small doses have a far longer period of violent convulsions and survive longer than those animals receiving relatively large doses. However, the muscular spasms in our intact cord dogs may to some degree hasten death. Studies of the blood chemistry of dying dogs have revealed no changes which could account for death.

All these facts led us to the conclusion that a lethal agent must be carried from the point of injection of toxin in the lumbar cord to some vital center. By transecting and by ligating the injected cord we have shown that the lethal agent does not pass up the spinal canal in the cerebrospinal fluid or within the substance of the cord itself.

We have explored the possibility that the small amount of toxin we inject is in some way multiplied to an amount sufficient to cause death. We have been able to show that such multiplication of the tetanus toxin molecule does not occur. Transplant experiments and assays show that the toxin is not multiplied and retained in the lumbar cord. Furthermore, the blood and lymphatic systems are the only remaining pathways by which the lethal agent can reach a vital center. If the toxin were multiplied and absorbed by the blood stream in amounts sufficient to cause death, there would be present such signs of general tetanus as trismus, opisthotonos, and muscular rigidity. These signs never appear in animals dying from injection of toxin into the cord.

Finally, death still occurs even though the blood and lymph contain large amounts of antitetanic serum throughout the entire course of the experiment. Obviously, if the toxin were multiplied and absorbed into the blood stream it would be neutralized by the antitoxin.

We therefore suggest (a) that tetanus toxin in the spinal cord is altered into a new lethal agent that is absorbed by the blood stream and is carried to some vital center where it has its lethal effect; and (b) that this new lethal agent is not neutralized by tetanus antitoxin.

The results of the injection of toxin into the medulla oblongata provide some additional evidence of this alteration, for even when toxin is injected into or close by vital centers in the medulla there is still a period of incubation and a period between the onset of symptoms and death. If death is due to the effect of *unchanged* toxin on the vital centers, death should come very much sooner than it does when toxin is placed in the medulla. Dogs receiving a solution of morphine sulphate in the medulla act very differently from the tetanus dogs. Within 15 minutes after the injection of morphine the respiration is depressed and signs of medullary irritation are present. These dogs have disturbances of deglutition which resemble the pharyngeal spasms of the tetanus dogs. The important fact is that after the injection of morphine these disturbances come on very much more quickly than after the injection of tetanus toxin.

The suggestion has been made by previous workers that tetanus toxin is altered into a different substance. Courmont and Doyon[15] thought that possibly the central nervous system symptoms of tetanus do not appear until the toxin has been changed into a strychnine-like body. Pohl, according to his assistant Zupnik,[16] said that tetanus toxin in striated muscle may be changed into a second body which causes death. Recently Zuger and Friedmann[17] have offered this same possibility as one explanation of some of their experiments. The earlier suggestions, however, having little experimental evidence to support them, went unheeded.

Alteration such as we have described would explain the experimental results of Abel and Chalian mentioned above, and would also explain the puzzling clinical finding that the use of tetanus antitoxin has not appreciably lowered the mortality rate of those patients who do not receive antitoxin until after the appearance of the central nervous system symptoms of tetanus.

We wish to emphasize the fact that the experimental work so far reported should by no means be interpreted as making unnecessary the use of tetanus antitoxin as a therapeutic agent in clinical tetanus. It is true that in dogs with experimental tetanus the administration of antitoxin is ineffective once a lethal dose has been fixed and symptoms of central nervous system tetanus are present. But since in human beings there is no way of telling whether a lethal dose has been fixed, the clinician should continue to use antitoxin in local or central tetanus in hopes that a lethal dose has not yet been fixed by the body tissues.

In discussing the cross-circulation experiments we must repeat that our

various control procedures have shown the cross-circulation itself to be harmless. Even marked differences in blood pressures and blood volumes are not sufficient to cause death. The cross-circulation experiments summarized in Table IX reveal that death of the donor due to medullary necrosis does not cause the death of the recipient. But death does occur in a significant percentage of the recipients cross-circulated with donors dying of tetanus, whether the toxin is injected intravenously or into the lumbar cord. We feel, therefore, that these experiments lend weight to our hypothesis that the tetanus donors absorbed into their blood streams some lethal agent sufficient in amount, in some instances, to kill the recipients. It is obvious, of course, that tetanus toxin *per se* could not have killed the recipients because in every case before the anastomosis was opened the recipient received much more than enough antitoxin to neutralize the toxin injected into the donor. No recipient ever exhibited any signs of tetanus.

One may well ask why every recipient did not die, especially since we injected into the donor's cord comparatively large amounts of tetanus toxin. We have mentioned before that in a long continued cross-circulation experiment the blood streams of both animals will eventually have equal concentrations of the formed and chemical elements in the blood provided that one animal is not receiving into its blood stream a steady supply of some element. But where, as in these experiments, one animal (the donor) is constantly absorbing into his blood stream some element (the lethal agent), the concentration of this element in his blood stream will be persistently higher than the concentration in the blood of the recipient. It is likely that the donor dies as soon as a fatal amount of this lethal agent is present. For these reasons one could hardly expect that in every instance the recipient also would receive a fatal amount before the donor dies.

In the second paragraph above, we have made a statement that requires further qualification. We should have said that death occurs in a significant percentage of the recipients *when* the cross-circulation is carried out under nembutal or when nembutal is given after the cross-circulation has been stopped, and even, in a small percentage, when no respiratory depressant is used. This brings up the question whether the lethal agent acts chiefly on the respiratory center. If this were true it might explain why the additional burden of nembutal was sufficient to kill so many of our recipients.

Our observations on the manner of death* of the animals in Experiment 1 suggested that possibly the respiratory center is that vital center on which the new lethal agent acts. It is also a common clinical observation that sudden respiratory failure is often the terminal event in patients dying of tetanus. If death is due to a poisoning of the respiratory center, it follows that toxin injected into or close to such centers should act more quickly and that to cause death a smaller dose should be required than in the case of injection into the lumbar cord. This we found to be true. When toxin is injected into the

* So constant was this manner of death that by watching the respirations we could almost always tell when death was near.

medulla oblongata death occurs twice as quickly, and a smaller dose suffices to cause death. After symptoms are present the injection of a usually safe dose of nembutal will kill the animal in a short time. We have also shown that when toxin is given intravenously the administration of enough nembutal or avertin to stop convulsions shortens life.

For these reasons, then, we think it likely that the respiratory center may be that vital center upon which the lethal agent acts.

Although the utmost care must be taken in applying to human beings the results of experiments on dogs, our observations on the manner of death and on the effect of respiratory depressants suggest that such drugs should be used with extreme caution in cases of human tetanus. This raises the question of using artificial respiration and respiratory stimulants in cases of human tetanus. It is interesting that, in the Johns Hopkins Hospital, there have been several cases of tetanus in which respiration has suddenly ceased and been restarted by artificial respiration. In one case respirations stopped and were started again eight times.

Further investigations on the problems mentioned in this paper are being carried on.

CONCLUSIONS

Experimental evidence has been presented to support the following statements:

(I) A small fraction of one lethal dose of tetanus toxin placed in a non-vital area of the central nervous system causes death.

(II) A similar dose of toxin in other organs of the body does not cause death.

(III) The principal factor causing death is not the metabolic changes consequent to the constant muscular spasms.

(IV) The lethal agent does not travel up the spinal cord.

(V) Death cannot be attributed to a multiplication of the tetanus toxin molecule.

These facts have led us to suggest that tetanus toxin in the spinal cord is altered into or liberates a different lethal agent which is transported to and has its lethal effect on vital centers.

Further evidence is presented which supports this suggestion and which makes it appear likely that:

(VI) The lethal agent is not neutralized by tetanus antitoxin.

(VII) The lethal agent may act chiefly on the respiratory center.

(VIII) The lethal action of this new substance may be enhanced by respiratory depressants.

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THYROID DISEASE IN A NONENDEMIC AREA

A THIRD SERIES OF OBSERVATIONS

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IN 1937, I reported observations on a second series of patients with thyroid disease treated at the Charity Hospital in New Orleans, increasing the total number of cases reported to 662 for the period from January, 1927, to July, 1936.[1, 2] I am now bringing this report up to date by adding 393 cases treated in the same hospital from July, 1936, to June, 1939, making a total of 1,055 cases for a period of nearly 12½ years. During this interval, there were approximately 590,000 admissions to the hospital, about half of which were surgical. I mention these last figures to emphasize again that thyroid disease is infrequent in this area.

Table I shows that the general mortality for the second and third series was the same and was only half as high as that reported in the first series. Further analysis of these figures in later tables reveals that in the third series there was an increase in the mortality rate in toxic patients as compared with that reported in the second series. The general mortality remained about the same because of an increase in the number as well as a decrease in the mortality of nontoxic goiters.

TABLE I

INCIDENCE AND MORTALITY OF THYROID DISEASE IN CHARITY HOSPITAL IN NEW ORLEANS

From January 1, 1927, to June 1, 1939

First series	341 cases	26 deaths	7.6%
Second series	321 cases	12 deaths	3.7%
Third series	393 cases	15 deaths	3.8%
Combined series	1,055 cases	53 deaths	5.0%

In Table II the cases are grouped as diffuse nontoxic, diffuse toxic, nodular nontoxic, and nodular toxic, following, as heretofore, the classification of the American Society for the Study of Goiter, a classification which I have found increasingly satisfactory from a clinical standpoint. It was noted in going over the records of the third series that there was more general adoption of this nomenclature by members of the various staffs. In view of the difficulty sometimes encountered in making a positive diagnosis in certain mildly toxic goiters even with the patient at hand, the difficulty of attempting to confirm or disprove the diagnosis simply from the charts is

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obvious. Consequently, unless there was definite collective evidence which pointed to a different diagnosis, the opinion of the historian with regard to toxicity or nontoxicity was accepted. Using this criterion, I found it necessary in a few cases, less than 10 per cent, to take the liberty of reclassifying the patients. In all instances this was a matter of transferring them from the toxic to the nontoxic group. In classifying the cases as nodular or diffuse, the original diagnosis, physical examination, operative notes and gross pathologic description were all taken into consideration, it being remembered that this classification is a purely clinical one.

TABLE II

DISTRIBUTION OF THYROID DISEASE IN CHARITY HOSPITAL IN NEW ORLEANS

Diffuse Nontoxic			
First series	87 cases	6 deaths	8.0 %
Second series	101 cases	1 death	0.99%
Third series	62 cases	0 deaths	0 %
Combined series	250 cases	7 deaths	2.8 %
Diffuse Toxic			
First series	94 cases	13 deaths	13.8%
Second series	61 cases	4 deaths	6.5%
Third series	84 cases	7 deaths	8.3%
Combined series	239 cases	24 deaths	10.0%
Nodular Nontoxic			
First series	77 cases	1 death	1.3%
Second series	99 cases	3 deaths	3.0%
Third series	191 cases	3 deaths	1.5%
Combined series	367 cases	7 deaths	1.9%
Nodular Toxic			
First series	83 cases	6 deaths	7.2%
Second series	60 cases	4 deaths	6.7%
Third series	56 cases	5 deaths	9.0%
Combined series	199 cases	15 deaths	7.5%
Total Nontoxic Cases			
First series	164 cases	7 deaths	4.2%
Second series	200 cases	4 deaths	2.0%
Third series	253 cases	3 deaths	1.2%
Combined series	617 cases	14 deaths	2.3%
Total Toxic Cases			
First series	177 cases	19 deaths	10.8%
Second series	121 cases	8 deaths	6.6%
Third series	140 cases	12 deaths	8.6%
Combined series	438 cases	39 deaths	8.9%

Examination of Table II reveals that for the combined series in nontoxic goiters there were approximately 1.5 times as many nodular as diffuse goiters, whereas in toxic goiters there were 1.2 times as many diffuse as nodular ones.

The mortality for the combined series of 617 nontoxic goiters was 2.3 per cent (Table II). In the third series, there was a definite decrease in the mortality of nontoxic cases, a decrease in the diffuse type from 8 per

cent in the first series to zero per cent in the third, while the mortality in the nontoxic variety remained about 1.5 per cent throughout the three series.

In the toxic cases, the mortality for the combined series was 8.9 per cent (Table II). In the diffuse group, the mortality in the second series (6.5 per cent) was half that for the first series (13.8 per cent), but in the third series the mortality was higher than that in the second group (8.3 per cent). In the nodular toxic group, the mortality in the first and second series was approximately the same, about 7 per cent, but in the third series there was an increase to 9 per cent.

To summarize, there has been a consistent improvement in the results obtained in the nontoxic patients subjected to operation. In the toxic group, the results in the second series were better than those in the first or third, but the mortality in all three series is still entirely too high.

TABLE III

RACIAL INCIDENCE AND MORTALITY OF THYROID DISEASE

First Series			
White	193 cases	11 deaths	5.7%
Negro	148 cases	15 deaths	10.1%
Second Series			
White	152 cases	3 deaths	2.0%
Negro	169 cases	9 deaths	5.3%
Third Series			
White	146 cases	4 deaths	2.7%
Negro	247 cases	11 deaths	4.4%
Combined Series			
White	491 cases	18 deaths	3.7%
Negro	564 cases	35 deaths	6.2%

An analysis of the racial incidence of thyroid disease (Table III) shows that in the first series white cases were 1.3 times more frequent than Negro cases, but in the third series the figures were reversed, there being 1.7 times as many Negro as white cases. The mortality in thyroid disease as a whole has been consistently higher in the Negro—in the first and third series, about 1.7 times as high; in the second, 2.6 times as high.

TABLE IV

RACIAL INCIDENCE AND MORTALITY OF TOXIC THYROID DISEASE

First Series			
White	104 cases	10 deaths	9.6%
Negro	73 cases	9 deaths	12.3%
Second Series			
White	71 cases	2 deaths	2.8%
Negro	50 cases	6 deaths	12.0%
Third Series			
White	58 cases	3 deaths	5.2%
Negro	82 cases	9 deaths	11.0%
Combined Series			
White	233 cases	15 deaths	6.4%
Negro	205 cases	24 deaths	11.7%

With reference to toxicity in the two races, analysis shows that 47.5 per cent of the total white cases and 36 per cent of the total Negro cases were toxic. The mortality in Negroes with toxic goiter has been higher than that in whites in each series, and about twice as high in the combined series, 6.4 per cent, as compared with 11.7 per cent (Table IV). This ratio in mortality was approximately the same when the toxic goiters of the third series were grouped as nodular and diffuse, as shown in Table V.

TABLE V

RACIAL AND SEX INCIDENCE OF DIFFUSE AND NODULAR TOXIC GOITER
THIRD SERIES

	Diffuse Type		Nodular Type	
	Operative Cases	Deaths	Operative Cases	Deaths
White male	10	1	2	1
White female	27	1	19	0
Total white cases	37	2 (5.4%)	21	1 (4.8%)
Colored male	5	1	4	1
Colored female	42	4	31	3
Total colored cases	47	5 (10.6%)	35	4 (11.4%)

In the third series, the mortality in white male patients with toxic goiter was 16.6 per cent and in colored males 22.2 per cent, as compared with 2.2 per cent in white females and 9.6 per cent in colored females (Table V).

I have expressed the opinion in former papers of this series that toxic thyroid disease when it occurs in the Negro in this community tends to be more severe and more grave than the same disease in white individuals, and offered as a possible explanation the tendency of the Negro to postpone medical consultation, particularly when pain is not an outstanding feature of his disease. Such delay is especially detrimental in toxic goiter in which, as we all now recognize, the best measure for lowering mortality is to treat the disease before the heart, liver and other organs have suffered severe damage.

Mortality is, as a rule, higher in toxic nodular goiter than in toxic diffuse goiter, but in our first series the mortality was distinctly higher in the diffuse group and in the last two series it was approximately the same. Why this difference exists I cannot say, but after analyzing the deaths, it seems likely that we have been better able to treat the complications resulting from prolonged toxicity, such as cardiac complications, pneumonia, liver damage and so on, but less able to prevent and treat crises, the more common cause of death in patients subject to this catastrophe.

I stated in my last report and repeat here that it has been very difficult to give our toxic patients adequate quiet and rest during the preoperative preparation. This situation has existed for a long time, but has been particularly acute during the past three years. In the fall of 1936, part of the hospital was demolished to clear a site for the erection of a new building and as a consequence there has been much noise and confusion and in-

creased crowding in the already overcrowded wards, both medical and surgical. Frequently it has been difficult to arrange for a patient with toxic thyroid disease to have a bed to himself, particularly in the Negro wards where "doubling-up" is so often necessary. During 1936–1937, when, perhaps, the confusion and crowding were at their height, 40 toxic cases were treated by operation, with a mortality of 15 per cent. During 1937–1938 and 1938–1939, there were 55 and 45 toxic cases respectively, with a mortality of about 6 per cent each year (Table VI). In retrospect, it is surprising that we fared as well as we did, although the high mortality rate is not attributable to this one factor alone. Four of the deaths among the toxic group and, certainly, the three deaths in nontoxic patients cannot be blamed upon the crowding and confusion incident to the building program.

TABLE VI

RACIAL AND SEX INCIDENCE AND MORTALITY OF TOXIC THYROID DISEASE
THIRD SERIES

	Toxic Goiter					Nontoxic Goiter					Toxic and Nontoxic
	Male		Female			Male		Female			
	White	Negro	White	Negro	Totals	White	Negro	White	Negro	Totals	
1936–1937 Operations	6	3	10	21	40	5	6	30	57	98	138
(July–July) Deaths	1	2	1	2	6	0	0	0	0	0	6
1937–1938 Operations	5	1	20	29	55	2	6	31	52	91	146
Deaths	1	0	0	2	3	0	0	0	0	0	3
1938–1939 Operations	1	5	16	23	45	5	3	15	41	64	109
Deaths	0	0	0	3	3	1	1	0	1	3	6
Total operations	12	9	46	73	140	12	15	76	150	253	393
Total deaths	2	2	1	7	12	1	1	0	1	3	15

In the patients of the third series, thyroidectomy was performed either because the goiter was toxic or was causing pressure symptoms, or, as in a few instances, because the patient wanted it removed for cosmetic reasons. There were still a very few instances in which, so far as I could tell from the records, the thyroid was removed simply because the patient had an enlarged gland and was in the hospital. It is interesting that many patients date their symptoms to a time when someone told them that they had a goiter or an enlarged neck. This frequency with which the development of symptoms is concomitant with the knowledge of a goiter's being present makes it difficult to diagnose thyroid disease of mild toxicity or to evaluate the rôle of the thyroid in causing pressure symptoms.

All toxic patients, whether the goiter was nodular or diffuse, were given iodine in some form as a preoperative measure and, as a rule, the period of administration was sufficiently long. Forty-six patients with nontoxic goiter, most cases of which were diagnosed as such by the staff operating on the patient, also received iodine as a preoperative measure. This, perhaps, is a manifestation of our lack of confidence in our differentiation of nontoxic from toxic goiter.

The fact that it has been impossible to insure adequate quiet and rest for many toxic patients has already been mentioned. The diet, except in a

few instances, was high in calories and carbohydrates. The importance of a diet adequate in proteins, especially in patients with great weight loss, has recently been emphasized. Attention is now being called to the use of vitamins, especially vitamin B-complex in the preparation of toxic patients. One important point generally neglected in this third series of cases was frequent recordings of the weight of toxic patients during preoperative preparation. In the absence of such records, it was difficult to estimate whether the diets were adequate or not, but I believe it likely that the high caloric diets offered were frequently insufficient for the very toxic patients.

There were some instances in which attempts to prepare the patients for operation were not persisted in over a sufficient length of time to induce a satisfactory remission.

The most commonly used sedative was luminal, bromide being next in frequency. Toxic patients with cardiac decompensation and those with auricular fibrillation were digitalized before operation. Quinidine was used preoperatively in one case. In two patients roentgenotherapy was employed as a preoperative measure; in one, the dosage seems to have been adequate, although there was too long an interval between roentgenotherapy and operation; in the second, the dosage was inadequate, only two exposures being administered.

In summary, it appears that there was an attempt to prepare adequately most of the toxic patients studied. Proper rest and quiet were particularly difficult to obtain, as already mentioned. The sufficiency of the diet is questionable, but the absence of weight recordings allows no definite conclusions with reference to this point. Whether toxicity was properly evaluated and whether the optimum time and the correct procedure were chosen is difficult to judge from a study of the records, particularly records which, although improved over those used in the two previous series, are not yet perfect. However, a study of the severe reactions following operation in some of the nonfatal cases and of the causes of death in the fatal ones leads me to believe that some patients were either not properly evaluated or were subjected to more surgery than they could bear.

In the three-year period covered by this last study, there were 415 operations performed on 393 patients. The fact that these operations were done by 48 different operators emphasizes again, as in the former series, that it is difficult for any one surgeon on this hospital staff to gain extensive experience in thyroid surgery and management. It follows, too, that it is impossible for interns, nurses, and anesthetists to become properly acquainted with the potentialities of thyroid disease and the seriousness of toxic goiter, yet it is well known that in the proper surgery of thyroid disease team work is an essential factor.

Of the 415 operations, 363 were performed under ethylene anesthesia and 36 under ether, the remainder under cyclopropane, local, or nitrous oxide. In only three cases was it recorded that avertin was used as a basal anesthetic.

Among the 140 toxic patients, 22 had two-stage operations; one of these patients died. Eighteen had only the first stage of an anticipated two-stage procedure; four of these patients died and 14 did not return for completion of the operation. One hundred had subtotal removal of the gland; seven of these died.

There were 253 nontoxic patients; of these 41 had lobectomies, 16 had simple enucleation of an adenomatous growth, and 196, of whom three died, had subtotal removal.

There was evidence in the records that 12 nonfatal cases suffered injury to the recurrent laryngeal nerves at operation; eight of these were nontoxic and four toxic. In half the cases the injury was bilateral.

Crile[3] has aptly said that it is easier to prevent than to treat the complications of hyperthyroidism. It is generally agreed that in the prevention of crisis, it may be wise to transfuse the patient immediately after operation; that an oxygen tent is invaluable; that morphine should be administered in adequate doses; that ice packs and other measures to decrease elevated temperatures should be used; and that an adequate intake of fluids and carbohydrates should be insured.

In reviewing the cases in this series, I found that transfusions were very rarely given. Oxygen tents are not always available in this institution and our patients cannot afford to rent them. Oxygen itself is always available, but often must be given by means of a nasal catheter. Crile points out that in the use of the oxygen tent the refrigeration obtained may be as important as the oxygen itself. In this series, morphine was ordered freely, but it is difficult to insure its being given frequently enough simply by leaving a p.r.n. order. Practically all toxic patients received intravenous saline and glucose postoperatively, but many received it in inadequate quantities. The majority received iodine postoperatively. I prefer to give iodine for at least a few days postoperatively, hoping to carry on the iodine routine so that no exacerbation of symptoms will occur because of its withdrawal.

A most important part of the postoperative regimen is watching carefully for signs of hemorrhage or tracheal obstruction. There was evidence that we have at times been lax in this respect, as three patients died from respiratory obstruction; these could perhaps have been saved by performance of tracheotomy at the proper time.

TABLE VII

CAUSES OF DEATH FOLLOWING OPERATION FOR TOXIC THYROID DISEASE

Laryngeal obstruction		2
Crisis		8
Operation during increase in toxic symptoms	4	
Presence of pneumonia at the time of operation	1	
Cause of crisis not determined	3	
Cardiac failure		1
Embolism		1

Analysis of the Deaths in the Third Series.—*Operative Deaths*: The 12 fatalities in the 140 toxic patients operated upon were analyzed in an attempt to determine the main causes of death. These causes are summarized in Table VII and include laryngeal obstruction, crisis, cardiac failure and embolism. It is possible that eight of these deaths were preventable.

There were three deaths in the group of 253 operations for nontoxic goiter. Two patients died from postoperative pneumonia and one from laryngeal obstruction.

Nonoperative Deaths.—In the third series, 23 nonsurgical patients with toxic goiter died. The race and sex of the patients as well as the type of gland present are indicated in the following summary:

Nodular toxic goiter:	1 colored male
	3 colored females
	2 white males
	2 white females
Diffuse toxic goiter:	3 colored males
	8 colored females
	1 white male
	3 white females

Here, as in the group of operative cases, we found about two Negro deaths to one white. The main causes of death in these cases were as follows:

Cardiac failure:	4 deaths
Pneumonia:	2 deaths
Crisis:	17 deaths

The following factors were considered precipitating causes of the crisis in eight of the fatal cases:

Extraction of teeth: 2 patients
Respiratory infections: 3 patients
Furunculosis: 1 patient
Suppurative parotitis: 1 patient
Fracture of femur: 1 patient

Eight of these deaths occurred between November and March and 15 between April and October. Rives and Sears,[4] of our staff, recently studied 21 instances of thyroid crisis occurring in nonsurgical patients, of which 16 crises developed during the months of June to October, inclusive. During these months, the temperature in New Orleans is consistently above 70° F., frequently above 90° F. The humidity here is consistently high throughout the year, only slightly lower in summer than in winter. These observers believe that the high temperature and humidity tend to embarrass the heat-regulating mechanism in toxic goiter, and that the increased frequency of thyroid crisis in summer is significant of that fact.

That our problem in thyroid disease is not peculiar to this institution is demonstrated in reports by Thompson and his co-workers[5] from Cook County Hospital of Chicago, an institution which is in many ways comparable to

ours. They reported that, in the years between 1931 and 1933, the mortality in exophthalmic goiter for the whole hospital was 13.1 per cent; in toxic adenoma 9.8 per cent; in nontoxic adenoma 4.1 per cent; and in simple goiter 2.6 per cent. These figures are comparable to ours. The second report of these authors covered the period from 1932 to 1937 and in it they compared the mortality of their own cases with that obtained in the remainder of the hospital, over which they exerted no control. In the control series, there were 572 toxic goiters with a mortality of 9.4 per cent; in their own series, there were 317 toxic goiters with a mortality of 2.8 per cent. In the nontoxic goiters, their mortality was half that in the control series. On the author's own services, they reduced the mortality rate in toxic goiters to one-sixth what it was previously. They summarize the regimen under which they succeeded in reducing the mortality rate as follows: Each patient was treated as an individual problem; surgery was withheld until the condition of the patient justified operation; a special high caloric diet for toxic patients was developed and operation was rarely performed unless the patient had gained weight; surgery was performed by a selected group of surgeons. These authors maintain that the policy of letting many surgeons get limited experience in operating upon patients with toxic goiter, together with the policy of keeping hospital beds free for use by quick turnover of these patients, will inevitably maintain a high mortality rate. With this I am in complete accord.

We note with some degree of consolation that Lehman and Shearburn[6] report a series of cases which embraces an experience similar to ours in Negro patients. Their figures show a 0.84 per cent mortality for white and 9.4 per cent for Negro patients with toxic goiter. This leads us again to our former conclusion that a disease is most a problem where it is least a problem. Our efforts must be directed to more adequate care, particularly in Negro patients.

SUMMARY

(1) Observations on 393 surgical cases of thyroid disease treated in the Charity Hospital in New Orleans between July, 1936, and June, 1939, are added to those of two previous reports, bringing the total number of cases to 1,055 for the period from January, 1927, to June, 1939. Of this total number, 491 are white and 564 are Negro patients.

(2) The mortality for patients with toxic thyroid disease in the third series, 8.6 per cent, is higher than that of the second but lower than that of the first series. However, in proportion there are twice as many toxic Negro patients in the third as in either of the other two series.

(3) Hyperthyroidism is a more grave and more severe condition in the Negro than the same disease in white individuals. The mortality is consistently higher in all series for Negro patients—1.3, 4.3, and 2.1 times higher in the first, second, and third series, respectively.

(4) The mortality rate for patients with nontoxic thyroid disease has

decreased from 4.2 per cent in the first series to 2.3 per cent in the third series.

(5) The preoperative preparation, the operative procedure and the postoperative care given patients in this series are analyzed and some of the factors contributing to the high mortality rate are pointed out.

(6) Fifteen deaths among the 393 surgical patients of the third series are analyzed, as well as 23 nonsurgical deaths that occurred in the same period of time.

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AUTOGENOUS TRANSPLANTATION OF A FIBROSARCOMA OF SKIN DURING THE APPLICATION OF A FULL-THICKNESS SKIN GRAFT

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FEW INSTANCES of auto-inoculation of human malignant tumors have been recorded in the literature in recent years. Instances of deliberate or unintentional transplantation of tumors to distant sites in the course of surgical procedures are extremely rare, and those reported involved chiefly carcinomata. The direct "seeding" of the operative wound or a serous membrane, and the dislodging of emboli to form distant metastases, in the course of operation for biopsy or removal of a tumor, have been recognized for many years. The dangers involved have been the subject of much bitter debate.[1, 2, 3] Accidental transmission to other individuals of viable malignant cell nests contained in aspirated fluids or incompletely killed vaccines have been reported.[4, 5] The most fascinating transplants are those in which the invasive cells appear to have been carried by the patient's hand, or to have been inoculated in a new site by the direct contact of an ulcerated malignancy with an uninvolved surface.[6, 7, 8, 9] Shattock and Dudgeon,[9] in 1915, reviewed the cases in the literature up to that time. Instances of transmission to other individuals, as by coitus, have been reported. Implantation of malignant cells in the wall of a viscus distal to the primary site, after having been carried by the contents of the organ or surgical instrument such as a bougie, has been recorded. The development of a second cancer *de novo*, or metastasis by the more common routes to a site of previously lowered resistance, must also be considered. Adequate microscopic study is often lacking in the older reports.

Two instances of successful, intentional human auto-inoculation of malignancies have been cited by Butlin[6]: (1) Portions of a disseminated carcinoma in the skin were transplanted by Hahn, in 1887, probably as a skin graft to uninvolved areas of skin; (2) a sarcoma of the breast was transplanted by Cornil, in 1891, to the opposite breast. The latter is the only instance of autotransplantation of sarcoma which we have discovered. The only previous instance of accidental transplantation in the course of skin grafting, which we have discovered, is that in which cells were transferred from the site of operative removal of a mammary carcinoma to a single

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donor area on the thigh during the application of pinch grafts to the skin defect.[10] Three cases of recurrence in skin grafts applied over incompletely excised tumors, one of which was a sarcoma, have been recorded.[11, 12, 13] The present case is, we believe, the second recorded instance of transmission of a sarcoma to a new site on the same individual as a result of an operation, and the first case in which a malignancy was transferred during the application of a full-thickness pedicle skin graft.

Case Report.—T. W. S., white, male, age 43, married, railroad brakeman, was seen in August, 1937, complaining of an ulcer on the heel for several weeks. The family history was negative for malignancy. The past history revealed no serious illnesses. Twenty-three years previously a freight car had run over the right heel, resulting in an avulsion of a portion of the os calcis. The wound healed slowly, but eventually became covered by skin. The patient continued to work, wearing a pad in the heel of the shoe. At intervals, usually during the summertime, the site of the old injury would break down but slowly heal again under local treatment, without the patient losing time at work. In the spring of 1937, he fell down some stairs, injuring the right heel, with subsequent development of an ulcer which gradually increased in size, discharged serous material, and failed to heal after local treatment.

The temperature, pulse and respirations were normal, the blood pressure 106/70. The patient was well developed, well nourished, and in no pain. The general physical examination was noncontributory except for palpable cervical and inguinal nodes and small varicose veins, more marked on the left leg. About one-third of the right heel was missing. In the skin overlying the site of the old injury was a 4 cm. round, firm, pink, ulcerated area, raised 0.5 cm. above the surface, fixed to the underlying tissues, and exuding a small amount of serous discharge. The Wassermann and other laboratory tests were negative.

A tentative diagnosis of osteomyelitis was made. On September 3, 1937, the granulating area was excised, and the exposed bone curetted; no infected areas were found. Microscopic preparations of the removed tissue showed little change in the stratified squamous epithelium. Fibrous strands, irregularly arranged, were separated by myxomatous tissue and were not sharply differentiated from the underlying stroma. The cells varied slightly in size, shape and staining quality, and contained small nucleoli. Some edema, with small numbers of polymorphonuclear leukocytes and lymphocytes, was present near the surface. A diagnosis of subacute inflammation of fibroelastic tissue was made elsewhere. A comparison of the tissue with that removed subsequently reveals that the process was invasive at this time. On September 23 and 30, 1937, the entire granulating area on the heel was covered with pinch grafts taken from the left thigh. The wounds healed completely and the patient was discharged from the hospital, October 6, 1937.

Two weeks later, thinning was noted in the grafted area, with two small ulcers at the outer margin. By November 11, 1937, two months after the first excision, the grafts had entirely disappeared and were replaced by clean granulation tissue. On November 12, 1937, the granulating area over the heel was again excised. A flap of skin the size of the exposed area of heel was dissected upward from the anterior surface of the left thigh with a very liberal pedicle attachment. The right heel was brought over to the left thigh, and the skin flap was sutured to the skin margins of the heel with silkworm-gut. Gauze and cotton packs were placed under the attached skin flap, as well as over the sutured skin edges, so that the margins of the granulating wound on the right heel could not come in contact with the skin of the left leg or the pedicle at the point of attachment to the left thigh. After padding, a plaster encasement was applied for eight days to hold the foot in position. An unusually abundant blood supply developed through the pedicle in that interval and the graft remained quite pink after

being severed. The V-shaped incision in the left leg was closed with a pressure dressing. No pathologic examination was made of tissue removed at this time. Both wounds healed satisfactorily; the graft on the heel retracted slightly at the skin edges over the upper aspect, but the blood supply remained ample. The patient was discharged, November 27, 1937.

During the next two months, the granulation tissue surrounding the graft on the heel definitely changed in character, becoming angry in appearance with greater vascularity and marked proliferation. It spread centrifugally from the margins to cover an area twice the former size; the extension could be noted from day to day. The graft was elevated above the surface by the proliferative growth and gradually shrank to half its original size. Local compresses with aluminum acetate and 1,200 R. units of roentgenotherapy were ineffective in reducing the granulations. Cultures for fungi were negative; a course of iodides gave no improvement. Severe pain developed in

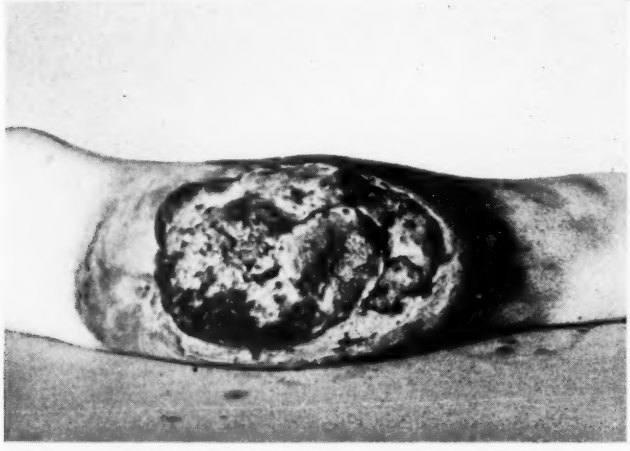

FIG. 1.—Right heel showing fungating mass and discolored skin. Note the shrunken skin graft to the right of the midline.

the heel and leg, requiring sedation. The patient was readmitted, January 26, 1938. In the five months since he was first seen he had lost a moderate amount of weight. The right heel was covered by a 12x9 cm. red, soft, friable, heaped-up, fungating mass which tended to overhang the border of nonulcerated skin and bled freely at the slightest touch. The skin for a distance of 3.5 cm. beyond the edge of the lesion was edematous and dusky purple in color. The well-preserved skin graft measured 4.5 cm. in diameter (Fig. 1). No nodes were palpable in the inguinal region. A diagnosis of fibrosarcoma was made from a biopsy of the heel.

On January 29, 1938, the right leg was amputated 10 cm. below the knee. Dense, white, firm tissue, distal to the graft and overlying the os calcis, appeared to be continuous with the bone; no other bone was involved. No necrosis was seen beneath the surface. The graft measured 0.8 cm. in thickness. Microscopically, the tissue was qualitatively similar to that previously seen—very vascular, made up of cells growing in strands and whorls undermining the squamous epithelium, and sharply demarcated from the underlying connective tissue (Fig. 2). The cells were very large, hyperchromatic, anaplastic, with large nucleoli and many mitoses. Definite areas of spindle and myxomatous cells with smaller nuclei were present. The tissue was found between spicules of bone, but did not invade tendon. At the junction of the old graft with the tumor many large vessels, most of which were thrombosed, were found, but no tumor emboli were demonstrated. Focal areas of slight lymphocytic infiltration were found deep in the tissue with polymorphonuclear exudate and gram-positive *Cocci* on the

surface only. The amputation wound healed promptly and the patient was discharged, February 12, 1938.

Shortly after discharge, the point on the left thigh at which the pedicle to the skin graft had been excised showed signs of infection, although no open wound had been

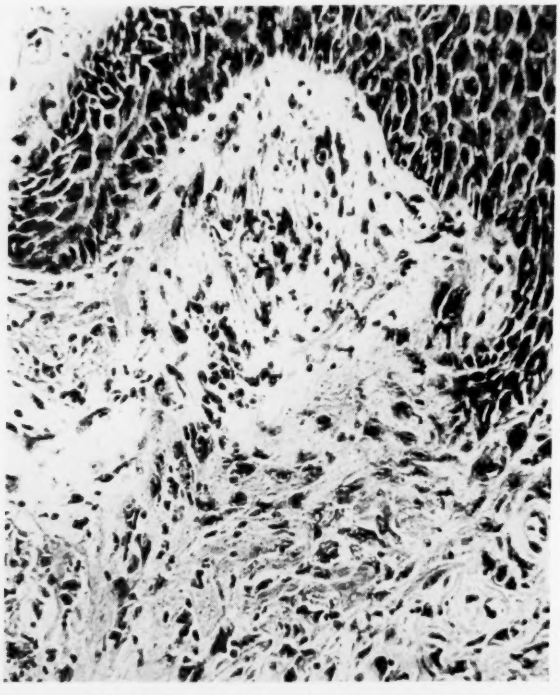

FIG. 2.—Photomicrograph of tissue from the right heel. (×110)

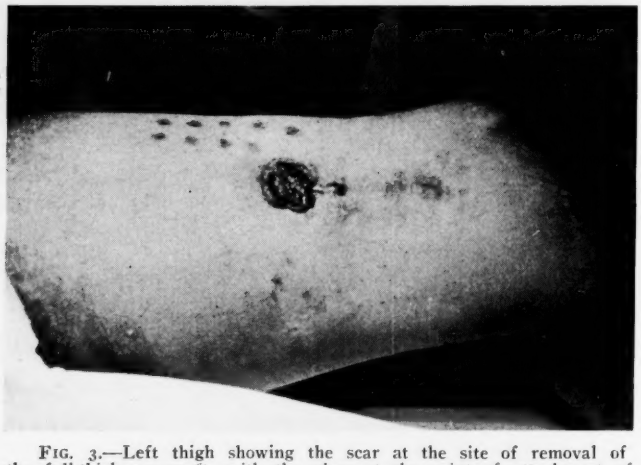

FIG. 3.—Left thigh showing the scar at the site of removal of the full-thickness graft, with the ulcer at the point of attachment of the pedicle. The scars of the previous pinch grafts are also visible.

present for three months. Warm saline compresses were employed with little benefit. A circumscribed ulcer 3 cm. in diameter developed, similar in appearance to the previous one on the right heel, with friable heaped-up edges, rising 4 Mm. above the surface and partly covered by epithelium. The base was pale, not granular, and was raised

above the surface of the surrounding skin (Fig. 3). On two occasions aerobic hemolytic *Staphylococcus aureus* and anaerobic *beta* hemolytic *Streptococcus* were cultured from this ulcer; mixed cultures of these organisms caused no lesion when injected into the skin of a rabbit. On March 12, 1938, an area of skin 7x4.5 cm. containing the ulcer together with the deep fascia overlying the muscle was excised. The floor of the ulcer was composed of white tissue, 4 Mm. in thickness, well demarcated from the underlying fat. Microscopically, the tissue was identical with that from the right heel, except for more anaplasia and increased numbers of mitoses—four to six per high power field (Fig. 4). Gram-positive *Cocci*, chiefly in phagocytes, were present only on the surface. At the growing edge, perivascular lymphocytic infiltration was present with

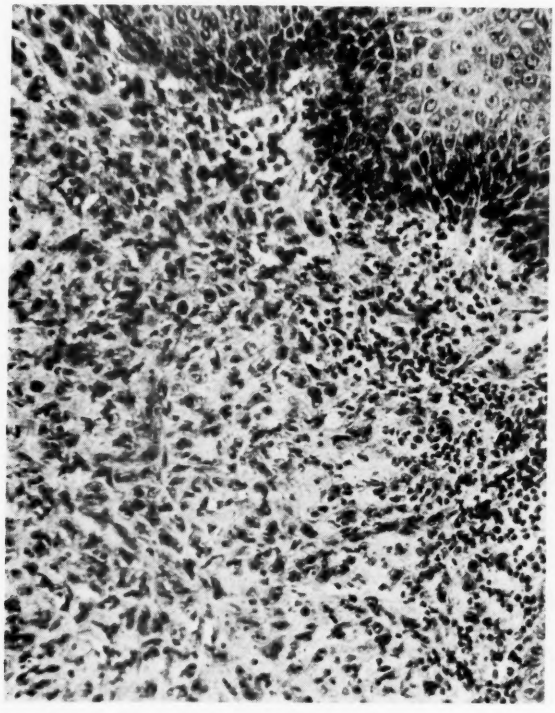

FIG. 4.—Photomicrograph of tissue from the ulcer on the left thigh. (×110)

a large amount of phagocytosed brown pigment, which gave a strong staining reaction for iron. The patient was discharged, March 20, 1938, with the wound well healed; no inguinal nodes were present. He received 1,800 R. units of roentgenotherapy postoperatively over the left thigh and inguinal region. Up to this time, December 20, 1938, there has been no sign of recurrence at either site, and the patient is up and about, using an artificial limb satisfactorily.

Comment.—The tumor in the present case apparently originated in granulation tissue by malignant change as the result of repeated traumata with secondary local infections over a period of 23 years. Bloodgood[14] has pointed out the difficulty in determining the malignancy of such tumors, particularly at the first examination.

It is possible that, by some unnoticed break in technic, tumor cells were carried, perhaps by the knife, from the malignancy on the heel to the upper end of the incision on the opposite thigh at the time the graft was raised

and applied. Contamination by direct contact during the time the two wounds were opposed seems less likely, for they were carefully isolated by dressings. In either event the transplant appeared at the site which was left intact for the preservation of blood supply to the graft. It would seem unlikely that cells were transferred later when the pedicle was excised, for the knife was used only on the "clean" area of the thigh and no sutures were taken.

Although sarcomata are known to spread chiefly through the blood stream, such an explanation is unlikely in the absence of other metastases. Since fibrosarcoma is highly invasive locally, but metastasizes slowly, direct extension is a possibility. Bloodgood,[14] however, points out that excision need not be carried far beyond the invading border to effect complete removal. This would suggest that such a possibility was a remote one in the present case, but two attempts at local excision were unsuccessful. The short time the graft was in contact with both areas would have necessitated a very rapid rate of growth for the tumor to pass by direct extension through either the lymphatics or blood vessels of the graft. However, rapid growth was noted clinically.

Handley[15] has advanced the theory and shown that carcinoma of the breast spreads chiefly by permeation of lymphatics. He has also traced the spread of a melanosarcoma of the skin of the leg for a distance of 17 cm., and believes the mode of initial spread in this tumor is identical with that of carcinoma. Davis and Traut[16] have described the growth of new blood vessels from the recipient area into grafts, and find them frequently growing up with great rapidity through thrombi in the transplanted vessels of the graft. By an analogous method, this sarcoma could have extended back through the pedicle graft to the donor area. Thrombosed vessels in the graft were demonstrated at the time of amputation, but no tumor cells were shown in them, although serial sections were not cut. It is possible that any tumor cells present were destroyed by increase in fibrous tissue; this has been noted in the experimental production of tumor emboli. It is impossible to tell which of the suggested routes of transfer is the correct one.

SUMMARY

An instance is reported of accidental autogenous transplantation of a fibrosarcoma of skin which developed in the scar of an old injury, following repeated traumata and infections. The transfer from the right heel to the left thigh was effected during the application of a full-thickness pedicle skin graft either by direct extension through the graft, or by accidental contamination of the incision at the donor site.

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BLOOD-BORNE PYOGENIC INFECTIONS OF BONES AND JOINTS*

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JOHN HUNTER, when asked by a pupil whether he had not, the year before, stated an opinion on some point directly at variance with one he had just put forth, is said to have replied: "Very likely I did; I hope I grow wiser every year." At another time, when asked whether he had written so-and-so, he replied: "Never ask me what I have said, or what I have written; but if you will ask me what my present opinions are, I will tell you."[1] These remarks are those of a sincere student of nature and are as applicable in the present day as they were some hundred years ago, for with the ever advancing knowledge of the medical sciences, we learn more of the underlying facts concerning the diseases of the human body as time goes on. In no other condition are these assertions more applicable than they are to that of acute hematogenous osteomyelitis, the conception of which has undergone constant changes during our lifetime.

Thirty years ago, the surgeon's endeavor in treating this disease was to eliminate, at once, the local focus from within the bone by means of some type of radical procedure. There were those who advocated the chiseling away of a surface of the cortex of the diaphysis and the removal of all the medullary contents by means of a curet; while others resected the entire diaphysis from within its periosteal covering. These were drastic, time-consuming operations which produced severe shock to patients already weakened by sepsis. If death was not hastened, a long convalescence was bound to follow, which terminated, only too often, in a crippled and deformed limb or an amputation. Gradually, we came to realize that the infection could not be eradicated at once, *en masse*, through these methods, and that the mutilating operative procedures added inestimable damage to an already embarrassed circulation of the bone, causing more bone necrosis than the disease itself.

The operative treatment of the bone lesion was much simplified by Starr,[2] in 1922, when he showed the actual manner in which the infection spread outward from the metastatic focus within the metaphysis. Because of his findings, Starr advised early, simple drainage of the focus; incision of the overlying soft parts until pus was found or, in cases in which the exudate had not as yet reached the subperiosteal space, the drilling of a few holes through the cortex of the metaphysis. This proved to be a decided advance in the treatment of the bone lesion as, by means of simple incision down to the abscess, adequate drainage is accomplished and tension is relieved

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without breaking down the local resistance of the tissues, or materially damaging the already embarrassed circulation to the bone. A further improvement in the treatment of the bone lesion was made by Orr,[3] in 1929, when he recommended adequate drainage of the lesion, packing the wound in the soft parts with vaselined gauze, and instituting complete rest of the part, through immobilizing the limb within a plaster encasement, and infrequent dressings. His recommendations, however, were slowly accepted, as the procedure was considered by many to be *unsurgical*. The results obtained by those who have employed Orr's method, however, more than establish its efficiency, and we believe that it is one of the greatest advances, so far made, in the treatment of acute inflammatory lesions of bone; for, through complete rest of the diseased part, not only from motion but also from the irritation of needless dressings, the local resistance of the tissues is enhanced, further spread of the infection is prevented, contamination by secondary organisms is precluded, pain is averted, and a state of complete muscular relaxation is obtained.

It is significant that none of the early writers on the subject of acute hematogenous osteomyelitis have laid sufficient stress upon the presence of an active blood stream infection. Starr dismissed the subject in these few words: "The blood stream infection is most frequently transient and cultures may be obtained but rarely. When the blood culture is positive and repeated, a general septicemia results, and recovery is uncommon." Orr says: "A patient with an acute bone infection and a septicemia already established (one might better say a severe septicemia since many of them, if not all, really have a septicemia from the beginning) calls for the exercise of great surgical judgment both at operation and subsequently. At the operation drainage is the essential thing; the operation must not stop short of it no matter where it leads one."

Finally, in 1934, Fraser,[4] of Edinburgh, drew our particular attention to the specific underlying condition of the acute osteomyelitis, that is, the blood stream infection. "A haemic infection of a bone," he said, "presupposes that staphylococcal organisms are already circulating in the blood stream and *that their localization in the bone is but a local manifestation of the general disturbance. . . . To the surgeon the local infection has been the important item in the clinical picture* . . . it is upon this that he has concentrated his ingenuity and his skill; *but is it right that we should regard the local focus as a most deplorable and regrettable manifestation? There is such a thing as a fixation abscess;—nature's method of producing a defensive area from which the factors of immunity are organized and developed.*"

This conception of the disease which we call hematogenous osteomyelitis places the bone lesion in a position of being merely an incidence in the course of a blood stream infection, which may be transitory or may continue until death claims the patient. We believe it is generally conceded that the blood stream infection, in many cases of this condition, is transitory and, therefore, the patient when first seen is often merely suffering from a localized abscess

involving the cancellous tissue of a bone and its surrounding soft parts or, in other words, an acute osteomyelitis. In these cases the treatment need only be directed toward the evacuation of the pus and to the promotion of the healing of the lesion; for the patient seldom dies of this single focus. New procedures for the improvement in the treatment must, therefore, be directed toward the so-called fulminating type of case, for in this type the patient is suffering primarily from the effects of the blood stream infection, a septicemia, accompanied by a local focus within a bone, which early in the disease is usually in its first stages of development. It is in this group of cases that the high mortality occurs, from septicemia, or from pyemia later in the course of the disease. In our experience, fatalities are almost always due to a septicemia or pyemia and never to the bone lesion (Table I). Pyrah and Pain[5] reached a similar conclusion through their studies of the post-mortem findings in 51 fatal cases. All these deaths could be ascribed directly to causes other than the bone focus, the result of a septicemia or a supervening pyemia with abscesses involving vital organs.

TABLE I

ANALYSIS OF 38 DEATHS IN A SERIES OF 218 CASES OF HEMATOGENOUS OSTEOMYELITIS

Causes of Death		
Septicemia:		
Staphylococcus	11	
Streptococcus	3	19
Unknown	5	
Pyemia:		
Staphylococcus	8	
Streptococcus	1	10
Unknown	1	
Pericarditis (Staphylococcus)		5
Endocarditis (Streptococcus)		1
Meningitis (Streptococcus)		1
Chronic sepsis		2
	Total	38

Evidently the mortality from this disease is not due to the osteomyelitis but to the preceding blood stream infection, which may cause death through a septicemia or pyemia. Thus, such endeavors that are made to save life should be directed primarily against the underlying blood stream infection, rather than concentrating them entirely upon one of the metastatic lesions which happens to be within a bone or joint.

Further, there is some question as to the advisability of too early drainage of the bone lesion. The advocates of early operation appear to be of the opinion that the disease arises within the bone and that all the systemic symptoms result from this focus; therefore, the earlier drainage is instituted the better it is for the individual. Those who view the bone lesion as an inci-

dence of the general blood stream infection believe, as Fraser does, that: "There is such a thing as a fixation abscess;—nature's method of producing a defensive area from which the factors of immunity are organized and developed," and further that: "The prognosis is improved if we have the courage to delay operation until the focus is reasonably well established and, having chosen the most opportune time, to restrict the operation to one involving the minimum of interference and yet securing drainage and relief of tension." Robertson,[6] a collaborator of Starr and until recently a strong advocate of early drainage, now states: "Recently, the writer has felt that an early operation gives no help to the patient. The problem in an early case

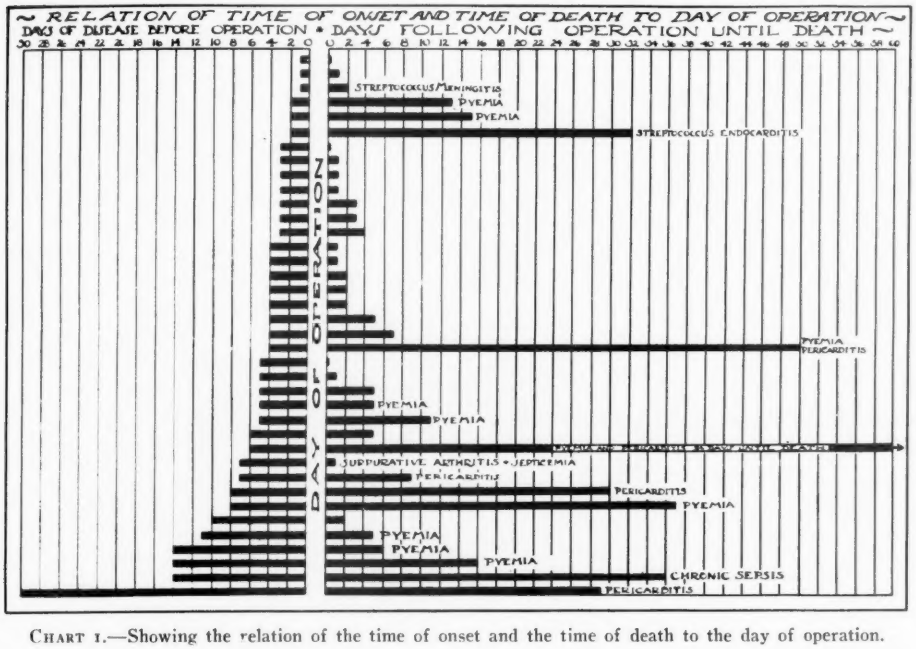

CHART 1.—Showing the relation of the time of onset and the time of death to the day of operation.

is one of combating a blood stream infection, dealing with the toxins and organisms that are present, and until some approach to an equilibrium has been reached surgery, in so far as incision of a local lesion goes, has nothing to offer. When the condition has reached a point where pus is present, then a simple drainage may be of advantage."[6]

We agree in general with the opinions expressed by both Fraser and Robertson, as five years ago, having reviewed our case histories, we discovered that 16 of the 38 deaths occurred before the third postoperative day and nine others before a week had elapsed (Chart 1). Thus 60 per cent of all the deaths in this series of 218 cases occurred during the first seven days following operation. Thirty of these children had been sick for less than seven days before operation and all were markedly septic. Three died as early as 24 hours following operation. It is useless to surmise as to how many lives might have been saved if the drainage of the focus had been

postponed until a time when the bodily resistance had increased sufficiently to combat the active blood stream infection. Some of these patients would have surely died from septicemia or pyemia, regardless of what procedure was followed, as the infection in many instances was overwhelming in its intensity; but in others we believe that more favorable results might have been obtained if operative intervention had been delayed, at least until the resistance of the body had been strengthened through the establishment of a physiologic fluid balance, as none of these patients received intravenous clyses before operation.

FIVE CASES ILLUSTRATING FULMINATING TYPES OF THE DISEASE, IN WHICH EARLY OPERATION WAS INEFFECTUAL

Case 1.—Staphylococcus Osteomyelitis of the Right Tibia; Pyemia. F. T., female, age nine, was admitted to the hospital, February 13, 1921. Five days previously, she had fallen down, subsequent to which she had walked a few steps but thereafter remained in bed, as she seemed to be getting steadily worse. On admission she was very toxic. Temperature 104.2° F., W.B.C. 28,000, polymorphonuclear leukocytes 87 per cent. There was marked swelling and tenderness over the right tibia, especially its lower end, and marked edema around the ankle.

The child was immediately operated upon. The periosteum was found entirely raised from the bone throughout its entire length by seropurulent fluid. The medullary cavity contained a small quantity of exudate of the same character. The anterior surface of the bone was cut away and the medullary cavity cleaned with a curet. Dakin tubes were inserted. Culture from the pus, as well as the blood culture, showed *Staphylococcus aureus.* A hypodermoclysis of 500 cc. was administered on the following day and another, of 450 cc., on February 15. At this time there was marked rigidity of the neck, the arms were held flexed and attempts to extend them caused pain. Hyperesthesia of the entire body was present. There was marked swelling with acute tenderness in the region of both parotid glands. On February 16, there was much more swelling of the parotid glands; the child died that afternoon, three days following operation and eight days after onset of the disease. Shortly after death a spinal tap showed clear fluid.

Autopsy.—Multiple abscesses in the heart muscle with patchy hyaline degeneration; injection of pia arachnoid of the brain; multiple abscesses of the lungs; acute parenchymatous degeneration of the spleen; acute parenchymatous degeneration and multiple miliary abscesses of the kidneys; acute parenchymatous degeneration and solitary miliary abscess of the liver.

COMMENT.—The pyemia in this case must have been present at the time of operation, three days before the death of the child, who had been sick for only five days at that time. Operation upon the bone focus could hardly be expected to be of help in this case.

Case 2.—Osteomyelitis of the Femur: E. D., male, age three, had been sick but two days, when admitted to the hospital, December 1, 1922. His condition was extremely toxic. Temperature was 105.2° F., W.B.C. 20,000, polymorphonuclear leukocytes 85 per cent. The region just below his left knee, which was held flexed, was swollen, hot and tender. The child was immediately operated upon, a three-inch incision being made along the lateral surface of the thigh, just above the condyle. The periosteum was found to be separated from the lower end of the femur and the space between it and the bone was filled with thin pus. The child died 12 hours later. There was no record of blood culture or culture of the pus. There were no roentgenograms taken.

COMMENT.—This was apparently a case of acute, fulminating osteomyelitis of the lower end of the left femur, with marked sepsis. The infection spread rapidly from the metaphysis to the subperiosteal space on the lateral surface of the femur. Death, which occurred 12 hours after operation, was due to septicemia, though pyemia may have occurred.

Case 3.—Staphylococcus Osteomyelitis of the Humerus. Suppurative Pericarditis: F. P., female, age nine, was admitted to the hospital, May 3, 1924. She had been ill for one week with pain in her left shoulder, which gradually became worse and the soft parts about the shoulder became swollen. There was high temperature and later pain in the left elbow. On admission, temperature 102° F., W.B.C. 19,800, polymorphonuclear leukocytes 80 per cent. The soft parts about the left shoulder were found to be tense and indurated and any motion at the joint produced pain. Signs of inflammation extended down the arm to the elbow joint. The capsule of the elbow joint was distended and fluctuant. The right arm was also swollen and painful. The child's condition was serious. She was delirious, dyspneic, and there was a pericardial friction rub which could be heard over the entire precordium.

The child was immediately operated upon. The periosteum was found stripped from the whole length of the left humerus. The bone was white and apparently dead. Pus, which was found infiltrating through all the tissues, was evacuated. Pus was also found under the periosteum of the right humerus. A *Staphylococcus haemolyticus* was recovered from the pus and from the blood cultures. The septic temperature continued and, May 17, the pericardial sac was aspirated and 140 cc. of thin, greenish pus was obtained. At the same time 200 cc. of straw-colored fluid was aspirated from the left pleural cavity. The culture from the pus showed *Staphylococcus haemolyticus.* Two days later, May 19, the pericardium was drained. The patient died, however, on June 3, 1924.

COMMENT.—In this case, we have an infection which localized in the proximal metaphysis of the left humerus and shaft of the right humerus, as well as in the pericardium. There was a definite bacteriemia during the entire time the child was in the hospital. Death was apparently due to the pericarditis, rather than to any localization of the infection in the bone.

Case 4.—Staphylococcus Osteomyelitis of the Femur. Suppurative Pericarditis: G. M., female, age 11, was admitted to the hospital, December 7, 1931. She had been ill for one week, the condition having started with a high temperature and pain in the region of the left hip joint. On admission, the child was delirious. Temperature 102.4° F., W.B.C. 15,800, polymorphonuclear leukocytes 86 per cent. The left hip was swollen and tender and the superficial veins over it were markedly dilated. There was little motion in the joint and any attempt to move it produced severe pain.

The child was immediately operated upon. The left hip joint was drained through an incision along the posterior border of the trochanter. A large amount of pus was evacuated. Cultures from the wound and the blood showed *Staphylococcus aureus.* On December 11, four days after admission, there were 500 colonies of bacteria per cubic centimeter of blood. The condition of the child grew steadily worse, though two transfusions were given, and, December 14, there were definite signs of an acute pericarditis. The patient died, December 16, 1931, nine days after admission.

COMMENT.—This patient was admitted in a state of sepsis and with a well-localized lesion of the left hip joint. There was no indication as to the portal of entry of the infection. *Staphylococcus aureus* was obtained from both the pus in the hip joint and the blood stream. The lesion apparently

started in the upper metaphysis of the neck of the femur and rapidly penetrated the bone into the joint. The child developed an acute suppurative pericarditis, which caused her death.

Case 5.—Staphylococcus Aureus Haemolyticus Pyemia; Acute Osteomyelitis of the Right Femur. Suppurative Arthritis of the Right Knee: N. C., female, age four and a half, was admitted to the hospital, February 5, 1933. One week previously, she had fallen on her right knee. Two days later, she complained of pain around the joint and her temperature rose to 105.2° F. On admission, the child was found to be extremely toxic. Temperature 104° F., W.B.C. 31,000, polymorphonuclear leukocytes 92 per cent. The region about the right knee was swollen and tender and motion caused extreme pain. There were signs of fluid in the joint. The knee joint was aspirated and 5 cc. of blood stained fluid was obtained, from which a hemolysing *Staphylococcus aureus* was obtained. The knee joint was drained and the limb was placed on a posterior molded splint. Culture from the blood showed many colonies of *Staphylococcus aureus.* The child's condition grew worse, though she was transfused on two different occasions. She died, February 10, 1933, five days after admission.

Autopsy.—Bilateral bronchopneumonia; serofibrinous pleurisy; fibropurulent pericarditis; fibropurulent peritonitis; focal abscess in the myocardia; acute vegetative endocarditis; focal suppurative necrosis of the liver; multiple abscesses of the ileum, cecum and ascending colon, with perforation of the ileum; multiple abscesses of the kidney. *Staphylococcus aureus haemolyticus* was obtained by culture from all of these lesions.

COMMENT.—There seems to be little doubt that, in this case, the osteomyelitis of the lower end of the femur was merely one of many metastatic lesions, which followed a *Staphylococcus aureus* blood stream infection. The autopsy showed the many lesions caused by this overwhelming blood infection. Death cannot be ascribed to the osteomyelitis and an earlier operation could hardly have been expected to save her life, as the pyemia developed so rapidly, for she was operated upon on the fifth day of the disease and died five days later.

The deaths were also studied in relation to the elapsed time of the disease before operation. In 128 instances, in which the children had been sick for less than a week, 30 died, a mortality of 23 per cent; while in the remaining 90 cases, in which the disease had lasted longer than a week, only eight died, a mortality of 8.9 per cent. The findings at operation in the former group were, in many instances, those of an early infection. The foci in 13 of these were entirely confined to a metaphysis, in five of which, only a few drops of thin, blood-stained exudate were obtained on drilling the cortex; and, in six others, though an exudate was found beneath the periosteum, it was serosanguineous in character. It is believed that the inflammatory focus within the bone, in many of these cases, had advanced so little that a definite abscess wall had as yet not been established and that, through postponement of the operation, at least until the water balance of the body had been increased, the local resistance of the tissues might have been increased. For the sake of argument in favor of this procedure, we present the modern practice of delaying incision of pyogenic infections of soft tissues until an

abscess has fully formed. Why, then, it may be asked, should a pyogenic infection of the medullary tissue of a bone be incised before it has consolidated as an abscess?

THREE CASES, ILLUSTRATING THE FINDINGS AT OPERATION, IN WHICH THE INFECTION HAD NOT AS YET BECOME LOCALIZED

Case 1.—Streptococcus Osteomyelitis of the Right Humerus. Septicemia: C. L., male, age eight, was admitted to the Pediatric Service, March 2, 1927. For five days, he had had pain in the right arm, which was accompanied by drowsiness and loss of appetite. His mother had noticed some swelling of the right arm for the first time on the day of admission, at which time his temperature was 106° F., pulse 124. The child was transferred to the Children's Surgical Service on the following day. At that time his condition was extremely toxic and he had severe, generalized convulsions. W.B.C. 15,000, polymorphonuclear leukocytes 90 per cent.

The patient was immediately operated upon, an incision being made over the anterolateral aspect of the upper end of the right humerus. The muscles were split and retracted. The periosteum was found to be edematous and raised. About one dram of thin, serosanguineous exudate was found beneath it. The cortex was drilled and about half a dram of material of the same character was obtained from the medulla. A small window was raised in the cortex. A second incision was made over the lateral aspect of the lower portion of the humerus. Here, the periosteum was found to be normal, but was incised and a hole was drilled and serosanguineous exudate obtained. The patient died within five hours after operation. Culture from the wound showed the *Streptococcus haemolyticus.*

COMMENT.—A case of acute, blood stream infection with an osteomyelitis of the right humerus, due to the *Streptococcus haemolyticus.* A thin, serosanguineous exudate was found at operation. The patient died five hours after operation. If the operation had been delayed until the body fluid had been replaced, would the outcome have been different?

Case 2.—Streptococcus Osteomyelitis of the Left Femur; Septicemia. M. C., male, age 11, was admitted, July 31, 1927, three days after he had returned from a two weeks' vacation in the country, apparently in perfect health. Twenty-four hours later, he complained of headache and went to bed. He soon began to have pain in the left inguinal region and left knee. His appetite was fairly good and there was no elevation of temperature. Bowels did not move. That night he was restless and apparently in pain. A slight epistaxis occurred during the night. The day before admission, he had a slight fever in the morning, which increased in the afternoon and he became delirious. He continued to have pain in the left groin, left knee and down to the left foot. He vomited once, the day before admission. On admission, the child appeared critically ill, with rapid respirations and delirium. Temperature was 106.4° F. The axillary nodes were enlarged, especially those on the left side. He complained of pain on movement of the left leg, referring it to the hip. Internal and external rotation of the left thigh caused no pain, but flexion and extension did.

An immediate operation was performed, a lateral incision being made through the skin and muscle just below the great trochanter down to the bone. A small quantity of clear, serous fluid was evacuated. The periosteum was loose, although not raised. Three drill holes were made through the cortex of the bone and were connected by chiseling. Sterile gauze packing was used and a dry, sterile dressing was applied. Culture from the wound showed *Streptococcus haemolyticus.* The child died on the following day, four days after the onset of the disease.

COMMENT.—This case is one of an early *Streptococcus haemolyticus* infection, with localization in the femur, which had not progressed to abscess formation.

Case 3.—Staphylococcus Osteomyelitis of the Right Tibia. Septicemia: J. K., male, age nine, was admitted to the hospital, December 21, 1927, four days after a fall, in which he injured his right knee. Twenty-four hours later he complained of severe pain in the upper part of the right leg and soon after he had a chill and vomited. His parents said he had fever. He continued to vomit and refused to eat. At the time of admission his condition was markedly toxic. Temperature was 106° F., pulse 140. There was swelling in the region of the right knee which extended up into the lower part of the thigh and down to the middle of the leg. The local temperature was increased and there was some redness of the overlying skin of the part. Motion at the knee joint was limited and painful and the entire area was tender. There was no maximum point of tenderness. W.B.C. 9,000, polymorphonuclear leukocytes 88 per cent.

He was immediately operated upon, an incision being made along the lateral aspect of the thigh, just above the external condyle of the femur. The periosteum was split and separated for a distance of about one inch and the bone was drilled. No pus was found. A second incision was then made over the anteromesial aspect of the tibia. Here the periosteum was found to be edematous and it separated easily. The metaphysis of the bone was drilled at this point, releasing a small amount of brownish-yellow pus under slight pressure. A small window was raised from the cortex and the wound was packed with gauze. One hour following the operation, the patient had a mild convulsion and died within four hours. Blood cultures taken at the time of operation showed no growth after 24 hours. Culture from the lesion showed the presence of *Staphylococcus aureus.*

COMMENT.—This case is of interest, as one of a severe septicemia with acute osteomyelitis of the metaphysis of the tibia. The child had been sick for only three days, and the lesion of the bone had not advanced to the state of abscess formation. The blood count indicated that there was little bodily resistance to the infection. The question arises whether the outcome might not have been different if the fluid balance of the body had been adjusted before operation had been undertaken.

Robertson,[6] who stated that "no case should be operated upon in which there is not a definite abscess," bases his conclusion on the supposition that the presence of the toxins from the local focus may stimulate the human organism to the production of antitoxin; and that "while a high degree of natural antitoxin may not be a factor in the direct destruction of the organism, yet it is not unreasonable to suppose that the neutralization of the toxin will allow other defense agents to have an unimpaired action in the destruction of the organisms."

Fraser[4] states: "I feel infinitely less anxious about the future of the osteomyelitis case when there is a pronounced local bone focus with early suppuration than I am when the local reaction is indefinite and suppuration is absent or delayed." From our own experience, we believe that nothing is to be gained through incision of an inflamed tissue in which the infection is still diffuse, but that when localization has occurred, the abscess should be drained.

It may be said by the advocates of early incision, that postponement of operation will increase the amount of bone necrosis, through intermedullary

tension and undue stripping of the periosteum by the exudates. This occurs in neglected cases. However, it is believed that during the time that the inflammatory process is consolidating, these factors are not active and that gross circulatory interference to the bone occurs only after the abscess has formed and commences to point.

It should become evident to anyone who studies a large number of cases that the course of acute hematogenous osteomyelitis differs materially in respect to the type of causative organism as it is found that the manifestations of the disease, when due to the *Staphylococcus aureus*, are quite different to those when due to the hemolytic Streptococcus. Though either type of organism may produce a septicemia or pyemia, accompanied by a local focus within a bone, the reaction of the body is quite different to each of these organisms; in fact, being caused by different organisms, each of these conditions is a separate, specific disease. Heretofore, little attention has been paid to the actual causative factor and, in consequence, in the past, the treatment of all cases of hematogenous osteomyelitis, whether due to the Staphylococcus or the Streptococcus, has been the same.

Robertson states that: "There is little similarity between the two conditions, and unless we make a clean cut distinction between Staphylococcus and Streptococcus osteomyelitis, there cannot be any clear understanding of the serologic problems that enter into the treatment of the condition. It is useless, from the standpoint of treatment, to group all cases of osteomyelitis and to consider the mortality of the whole group." The difference in the two diseases, he says, is due entirely to the nature of the toxin of the Staphylococcus and its ability to produce necrosis, and that the Staphylococcus may have recurring attacks, while the Streptococcus never does.

In the early part of 1933, soon after reviewing our previous cases of acute osteomyelitis, we began to make modifications in the manner of handling these cases. Since then, through the gradual introduction of improved methods, a more conservative form of procedure has been established in caring for these patients, as we began to treat the individual patient, rather than using a routine procedure in all cases.

These changes may be briefly outlined as follows: On admission of the patient to the hospital, a tentative diagnosis being made, the individual's general physical condition is built up through the administration of intravenous clyses of a solution of normal saline, with 5 per cent glucose, and blood transfusions, when indicated. In order to ascertain the type of organism responsible for the condition, a blood culture is taken at this time and samples of exudates from joint effusions or superficial abscesses, if present, are obtained for bacterial investigation. The involved limb in the meantime is completely immobilized in splints or by a plaster encasement. When the fluid equilibrium of the body is established, which should be accomplished within six to 18 hours, the question of draining the lesion may be considered. In the presence of a well-formed abscess in the soft parts or a pyarthrosis with

thick pus, operation is not further delayed. If, however, a thin exudate has been obtained through aspiration, or the causative organism has been shown to be the *Streptococcus haemolyticus*, operation is postponed, though a distended joint is always emptied of its effusion by aspiration before the limb is immobilized. An active focus can be cured in some instances through immobilization of the part and, in others, the inflammation becomes localized and makes the establishment of drainage at a later date easier and more efficient. Sulfanilamide should be given in those cases in which the *Streptococcus haemolyticus* is shown to be the causative agent. (There were three cases in our series in which it was used.)

A CASE ILLUSTRATING THE USE OF IMMOBILIZATION OF THE LIMB AND DELAY OF OPERATION UNTIL THE INFECTION BECAME LOCALIZED

Case Report.—Streptococcus Osteomyelitis of the Femur. Pyarthrosis of the Hip: R. A., male, age ten, was admitted, June 1, 1937, with a five day history of pain and swelling around the right hip joint. He had had drainage from the right ear for several months. The boy was acutely ill, with a temperature of 105° F. He was dehydrated. There was swelling and marked limitation of motion of the right hip joint. The hip joint was aspirated and thin pus was obtained. *Streptococcus haemolyticus* was cultured from the pus. A blood culture at this time was positive for *Streptococcus haemolyticus.* The fluid balance of the patient was restored and several small blood transfusions were given. The right hip was immobilized by means of a plaster spica. For three and one-half weeks the boy remained acutely ill, with a septic type of temperature. Sulfanilamide was given during this period. Then his general condition improved and the temperature subsided. Several changes of the plaster spica were made during the following five months. Whenever the spica was left off for a few days, however, there would be a rise in temperature, during this period.

Five months following admission, fluctuation developed over the upper third of the right thigh, accompanied by a rise in temperature. This area was incised and drained, a few sequestra were removed, and a plaster spica reapplied. The boy remained in the hospital for another six months and was discharged with the wound healed. Roentgenograms at this time showed marked destruction of the femoral head and neck. There was some loss of function of the right hip. At the present time, the wound is healed. There is still some loss of motion of the hip joint, though ankylosis is not present.

COMMENT.—Though limitation of motion is still present, the destruction of the head and neck was not great, as compared with other cases of the *Old Series* treated by traction, where secondary infection so often ensued.

The operative procedure which is employed is as simple as is consistent with the establishment of adequate drainage which must be obtained, wherever it leads one. The most direct route of approach to the lesion is chosen by ascertaining the maximum point of tenderness before the anesthetic is administered. The incision through the soft tissues must be ample enough to expose the underlying bone. If pus is found beneath the periosteum, the membrane is widely incised without stripping it further from the bone. If no pus is found, the periosteum is incised over its most edematous part and the edges are carefully pushed apart with an elevator, exposing a small area of the cortex of the metaphysis. The cortex is then drilled in several places with a quarter-inch bit, or a small "trapdoor" is raised with a gauge. The

cancellous bone of the metaphysis should not be disturbed. The edges of the wound in the soft tissues are then gently packed apart with vaselined gauze and the wound is dressed with a copious dressing of dry gauze, after which a plaster encasement is applied to the limb. This should extend well beyond the joints contiguous to the involved bone, so as to obtain complete immobilization of the part as any slight motion within it, by causing pain, will hinder the relaxation of the tense muscles about the lesion. Suppurative joints are drained in a similar manner, the capsule being widely incised in one or more places. (A pyarthrosis of the knee joint, for example, is drained through two parallel incisions, one on either side of the patella.) The edges of the wound in the overlying soft tissues are then packed apart with vaselined gauze, care being taken not to place any within the joint cavity. The wound is then dressed and the limb is immobilized in a plaster encasement. Though most cases of Staphylococcus pyarthrosis are due to the direct extension from a focus in a neighboring metaphysis, experience has shown us that the drainage of the joint is adequate in relieving the metaphyseal lesion, as has been reported.[7] The encasement must not be removed until odors from the dressings become offensive, nor should a window be cut in it for inspection or dressing of the wound. Orr[3] states that: "Following operation, with a sick patient, the desire to be doing something often leads to excesses of treatment that are undesirable. Even if all the symptoms persist following such an operation, nothing is to be gained by further disturbance of the wound. Dressings, which are nearly always resorted to, should, therefore, not be done." To this we thoroughly agree.

Following operation, the general physical condition of the patient must be improved, through careful nursing and attention to the physiologic needs of the body. During the early days, the water balance and nutrition must be stabilized through venous clyses of normal saline and glucose and a simple, nutritious diet. Blood transfusions are most important for increasing bodily resistance.

Since employing this procedure, in the treatment of acute hematogenous osteomyelitis or pyarthrosis, we have cared for 50 children with one or the other of these conditions, though complete immobilization was not used in the earlier cases. We are, therefore, able to compare the results obtained in these cases with those of our former series, in which more radical methods of treatment had been used routinely, without preoperative preparation of the patient. Though the number of cases in the *New Series* is small, compared with those of the *Old*, the improvement shown in the results is so striking that we believe we may report our findings to advantage.

The causative organisms are known in 185 of the 218 cases of the *Old Series*, and in all of the 50 cases of the *New Series* (Table II).

The mortality of the *Old Series* was 16.7 per cent, and that of the *New* 10 per cent.

In cases with positive blood cultures, the mortality of the *Old Series* was 46 per cent, and that of the *New* 29 per cent.

The mortality of cases of infection due to the Staphylococcus of the *Old Series* was 16.5 per cent and of *Streptococcus haemolyticus*, 17 per cent; while in the *New Series* it was Staphylococcus, 10.3 per cent, and *Streptococcus haemolyticus*, 9.5 per cent.

In cases with positive blood cultures, the mortality of those cases due to Staphylococcus of the *Old Series* was 46.5 per cent and of *Streptococcus haemolyticus*, 44.5 per cent; while in the *New Series* it was Staphylococcus, 27 per cent, and *Streptococcus haemolyticus*, 33.3 per cent.

TABLE II

TWO SERIES OF CASES OF OSTEOMYELITIS, IN WHICH THE MORTALITY OF THE MORE CONSERVATIVE METHOD IS COMPARED WITH THAT OF OLDER METHODS

	Old Series						New Series					
	Culture from Focus			Positive Blood Culture			Culture from Focus			Positive Blood Culture		
Type of Organism	No. of Cases	Deaths	Per Cent	No. of Cases	Deaths	Per Cent	No. of Cases	Deaths	Per Cent	No. of Cases	Deaths	Per Cent
Staphylococcus	151	25	16.5	41	19	46.5	29	3	10.3	11	3	27.0
Streptococcus	34	6	17.0	9	4	44.5	21	2	9.5	6	2	33.3
Totals	185	31	16.7	50	23	46	50	5	10	17	5	29

There were five deaths among the 50 cases of the *New Series*. Three of them occurred in cases of infection due to the Staphylococcus and two due to the Streptococcus.

Eleven patients with Staphylococcus osteomyelitis, two of whom had complicating pyarthrosis, were treated by immediate immobilization in a plaster encasement following operation (Table III). One of them died two months later from a Staphylococcus meningitis, following an acute middle ear infection and mastoiditis. Eight other patients with Staphylococcus osteomyelitis, two of whom had a complicating pyarthrosis, were treated with plaster encase-

TABLE III

LOCAL TREATMENT OF STAPHYLOCOCCUS CASES

Procedures	No. of Cases	No. of Deaths	Cause of Deaths
Orr technic	11	1	Two months after operation, Staphylococcus meningitis following mastoiditis
Encasement immobilization 2 wks. after operation	8	0	
Immobilization in splints after operation	8	2	(a) Five months later—pyemia (b) Four days later—pyemia
Carrel-Dakin treatment	2	0	
Totals	29	3	

ments which were applied within two weeks following the operation. None of these died. Eight patients with Staphylococcus osteomyelitis, one with a pyarthrosis, had the involved limb immobilized by means of molded plaster splints immediately following operation, in order that the wounds might be

dressed from time to time. Two of them died; one, five months after operation, from multiple secondary foci; and the other, four days following operation, from a pyemia, with abscesses involving almost all the vital organs. The two remaining instances of patients with Staphylococcus osteomyelitis were treated by the Carrel-Dakin technic without any fatality.

SEVEN CASES OF STAPHYLOCOCCUS OSTEOMYELITIS ILLUSTRATING THE MORE CONSERVATIVE TREATMENT OF THE FULMINATING TYPE

Case 1.—Staphylococcus Osteomyelitis of the Tibia: T. L., male, age four, was admitted, April 24, 1933, with a three-day history of pain and swelling around the right knee, following an infected blister of the right heel. Temperature 106° F., W.B.C. 25,000, polymorphonuclear leukocytes 96 per cent. The day of admission, after receiving intravenous clyses, the right tibia was drilled, Carrel-Dakin treatment was instituted and a splint applied to the right thigh and leg. Culture of the pus obtained was positive for *Staphylococcus aureus.* Following operation, another foci developed in the upper end of the right humerus, which had to be drained four days later. At this time a blood culture was positive for *Staphylococcus aureus.* Following incision and drainage of the right humerus, a plaster shoulder spica was applied. He remained in the hospital for four months, being discharged August 15, 1933. At the time of discharge the wound over the tibia was still draining. Unfortunately, he never returned to the Follow-Up Clinic.

COMMENT.—This case illustrates that the primary Orr treatment of the osteomyelitis of the humerus was followed by prompt healing, while the Carrel-Dakin treatment of the tibia was not.

Case 2.—Staphylococcus Osteomyelitis of the Os Calcis: I. P., female, age nine, was admitted, July 15, 1933, with a three-day history of pain in the right heel. Temperature was 105° F. Two days later, the soft tissues over the right heel were incised. A blood culture at this time was positive for *Staphylococcus aureus.* Following operation the temperature remained high. Four weeks later, the os calcis was split and a plaster encasement applied. This was continued for three months, at which time the wound was healed. She was discharged December 3, 1933. When seen in the Follow-Up Clinic, one year later, the wound had remained healed.

COMMENT.—This case illustrates conservative treatment of a fulminating case of osteomyelitis, though the Orr treatment was not employed until the os calcis had been opened.

Case 3.—Staphylococcus Osteomyelitis of the Radius, with Multiple Other Foci in Bones. Pyemia: J. K., male, age eight, was admitted, November 21, 1933, with a 24-hour history of abdominal pain. The physical findings noted were tenderness and spasm in the right side of the abdomen. Temperature, 104° F., W.B.C. 12,100, polymorphonuclear leukocytes 70 per cent. For two days, the patient was observed in the hospital and then an appendicectomy was performed. The appendix was not diseased. The day following this operation, pain was complained of in the left wrist and, four days later, the wrist was incised and drained. Culture from the pus obtained was positive for *Staphylococcus aureus.* At this time the blood culture was also positive for the same organism. Following this, foci developed in the proximal end of the right tibia, the proximal end of the right femur, the proximal end of the left tibia and the distal end of the left humerus. Each focus was incised and drained and splints applied to the extremities affected. Two and one-half months after admission, he developed a unilateral empyema and a purulent otitis media. Cultures from both were positive for *Staphylococcus aureus.* After four and one-half months, the temperature dropped to normal and remained so. The boy remained in the

hospital for eight months more. On discharge, December 16, 1934, all wounds were healed. When seen in the Follow-Up Clinic, four years later, the only deformity was a fusion of the right hip, with two inches' shortening of the right lower extremity.

COMMENT.—This case illustrates an osteomyelitis with pyemia which recovered. Though the Orr technic was not then employed, the involved limbs were immobilized with plaster splints and the fluid balance of the body was kept up.

Case 4.—Staphylococcus Osteomyelitis of the Left Tibia: N. W., female, age two and one-half, was admitted, April 28, 1935, with a two-day history of pain around the left ankle. Temperature 104° F., W.B.C. 11,500, polymorphonuclear leukocytes 85 per cent. Twenty-four hours following admission, her fluid balance having been adjusted, the lower end of the left tibia was drilled, the wound lightly packed with vaselined gauze, and a plaster encasement applied. The blood culture at this time was positive for *Staphylococcus aureus.* The Orr method of treatment was continued for two months, when a sequestrectomy became necessary. A month following this, the child was discharged, September 21, 1935, with the wound healed. She has not returned to the Follow-Up Clinic.

COMMENT.—A case of the fulminating type of osteomyelitis, with a bacteriemia, treated by the Orr technic without further foci in either bone or soft tissues.

Case 5.—Staphylococcus Osteomyelitis of the Tibia: R. P., male, age five, was admitted, March 18, 1938, with a three-day history of pain in the right leg. There was swelling and tenderness over the proximal end of the right tibia. Temperature 105° F., W.B.C. 11,500, polymorphonuclear leukocytes 80 per cent. The blood culture taken at this time was positive for *Staphylococcus aureus.* Several hours following admission, after the administration of intravenous fluids, he was operated upon. The wound was lightly packed with vaselined gauze and a plaster spica applied to the extremity. Following this procedure, the temperature gradually subsided, so that 20 days later it remained at a normal level. During this period one blood culture was positive for *Staphylococcus aureus.* The Orr method of treatment was followed for five months, when a roentgenogram showed a sequestrum. This was removed and the Orr method continued. Four months later it was necessary to saucerize the old cavity, which was followed by healing.

COMMENT.—This patient was treated by means of the Orr technic throughout; though he had a blood stream infection, no other foci developed in either bone or soft tissues.

Case 6.—Staphylococcus Osteomyelitis of the Right Tibia. Pyarthrosis of the Right Knee: B. S., female, age 14, was admitted to the Fourth Medical Division, December 22, 1937, with a three-day history of pain and swelling of the right knee. Temperature 104° F., W.B.C. 10,500, polymorphonuclear leukocytes 80 per cent. A provisional diagnosis of acute rheumatic fever was made. She remained on the medical ward for five days, when a definite diagnosis of acute osteomyelitis of the lower end of the right femur was arrived at. At this time, the blood culture was positive for *Staphylococcus aureus.* Her temperature fluctuated daily between 102° and 104° F. On December 28, she was operated upon. A considerable quantity of pus was drained from the soft tissues of the upper end of the right tibia. The periosteum was elevated and pus was found beneath it. The wound was packed with vaselined gauze and a plaster encasement applied to the thigh and leg. The organism cultured from the pus was *Staphylococcus aureus.*

Following the operation, her temperature dropped to about 101° F. and remained at this level for two months. The postoperative treatment consisted of repeated blood trans-

fusions and supportive measures, along with immobilization of the extremity by means of a plaster encasement extending to the hip. Several blood cultures were negative. Two months following the operation, the temperature rose to a level of 104° to 105° F. The old wound was opened and further drainage of the tibia was instituted by the removal of some necrotic bone. The wound was lightly packed with vaselined gauze and an encasement applied to the thigh. This was followed by a spread of the infection into the knee joint. The knee joint was then drained by means of two lateral incisions. These wounds were lightly packed with vaselined gauze and a plaster encasement was applied from the toes to the chest. At this time the blood culture was again positive for *Staphylococcus aureus.* Four days following drainage of the knee joint and the application of the plaster spica, the temperature fell to below 100° F. and remained there. Several changes of the spica were made and she was discharged, July 2, 1938, with the leg and thigh immobilized. She now has an ankylosed knee joint and there is a small sinus over the upper end of the tibia, which occasionally heals, only to later break down.

COMMENT.—This patient was seen, for the first time, in consultation, two months after the initial drainage, when her blood stream became positive for the second time. The case demonstrates the necessity of efficient drainage, as following the incision of the knee joint and the use of complete immobilization, the blood stream infection ceased and the temperature rapidly returned to normal.

Case 7.—Staphylococcus Osteomyelitis of the Left Femur: T. A., male, age 16, was admitted, September 8, 1939, with a three-day history of pain and swelling of the right index finger. Temperature 102° F., W.B.C. 11,200, polymorphonuclear leukocytes 75 per cent. The right index finger was reddened and swollen over the entire dorsal surface.

The day following admission, the finger was incised and drained. However, the temperature remained elevated and, two days later, the patient complained of pain over the lower end of the left thigh. Swelling and tenderness developed over this area and, three days later, the region was incised and drained. Pus was found beneath the periosteum of the lower end of the femur. The wound was packed with vaselined gauze and a posterior molded splint was applied in an attempt to immobilize the leg. Intravenous clyses were given. Cultures from pus of the finger and the thigh were positive for *Staphylococcus aureus.* The culture from the blood was also positive for the same organism. The patient's temperature remained elevated around 104° F. and, five days following drainage of the infection of the femur, a plaster spica was applied. Following this, there was a drop in temperature to a level of about 102° F. and, eight days later, the blood culture was negative for Staphylococci. In the meantime, he had developed an abscess of the right antecubital fossa, which was drained. The right arm was immobilized by means of a plaster encasement. This was followed by a gradual drop in his temperature and gradual improvement in his general condition. Repeated blood transfusions were administered during this period, as well as intravenous clyses. Three months following operation, the encasement was removed, and a month later the patient was discharged. At the present time there is slight drainage from the wound in the thigh. He also has a chronic osteomyelitis of the phalanx of the finger.

COMMENT.—This case demonstrates the fulminating type of osteomyelitis with a positive blood stream infection, where there was fairly rapid improvement without metastases to other bones, following the employment of the Orr treatment.

Of the cases of Streptococcus infection (Table IV), seven patients, two of whom had a pyarthrosis of the hip, were treated by immobilization of the

involved limb in a plaster encasement immediately following operation, with no fatalities. Two others, who had plaster encasements applied within two weeks following operation, recovered. In the cases of five patients whose limbs were immobilized in molded splints following operation, one died on

TABLE IV

LOCAL TREATMENT OF STREPTOCOCCUS CASES

Procedures	No. of Cases	No. of Deaths	Cause of Deaths
Orr technic	7	0	
Encasement immobilization 2 wks. after operation	2	0	
Immobilization in splints after operation	5	1	Twelve days after operation—emboli with gangrene of feet
No immobilization	3	1	Seven days after operation—from old lung abscess
Encasement immobilization—no operation	4	0	
Totals	21	2	

the twelfth postoperative day from multiple emboli of the vessels of the lower extremity. In three cases, no immobilization was used at all; one of these patients died of a lung abscess which was apparently the portal of entry of the blood stream infection. In four instances, two of which were pyarthroses of the hip, the lesions resolved without operation, the limbs being merely immobilized in plaster, following aspiration of the effusions.

TWO CASES OF STREPTOCOCCUS OSTEOMYELITIS ILLUSTRATING THE MORE CONSERVATIVE TREATMENT OF THE FULMINATING TYPE

Case 1.—Streptococcus Osteomyelitis of the Tibia: B. K., male, age one and one-half, was admitted, January 2, 1933, with an eight-day history of pain and swelling of the right leg. These symptoms were preceded by an upper respiratory infection. On admission, there was considerable swelling over the proximal third of the right tibia. Temperature 105° F., W.B.C. 18,000, polymorphonuclear leukocytes 80 per cent. A blood culture taken on admission was positive for hemolytic Streptococcus. Twenty-four hours after admission, the soft tissues over the proximal end of the tibia were incised and drained. Thin pus was found beneath the periosteum. The bone was not drilled. Following the operation the leg was immobilized by means of a posterior plaster splint. The patient's clinical condition gradually improved and, 14 days later, the temperature reached a normal level. Within six weeks the wound was healed. The boy was discharged, February 17, 1933, but he did not return to the Follow-Up Clinic.

COMMENT.—A case of Streptococcus osteomyelitis with blood stream infection, treated by drainage of the focus and immobilization of the limbs by means of plaster splints.

Case 2.—Streptococcus Osteomyelitis of the Femur: F. G., female, age 14 months, was admitted, February 6, 1933, with a two-day history of pain in the right thigh. Three weeks previously she suffered from a "cold" and her mother stated that she had had no appetite since. On admission, there was tenderness over the distal end of the right femur.

Temperature 104.8° F., W.B.C. 26,600, polymorphonuclear leukocytes 78 per cent. A blood culture taken at this time was positive for hemolytic Streptococcus. On the day of admission, the soft tissues over the lower end of the femur were incised, after the fluid balance had been adjusted, but no pus was encountered. The bone was then drilled and a few drops of thin, purulent material obtained. Carrel-Dakin tubes were placed in the wound and the leg immobilized by means of a posterior plaster splint. Following this procedure, her postoperative course was characterized by a high temperature and complicated by ulcerations of both buttocks. However, at the end of a month, the temperature had reached a normal level and she was allowed to leave the hospital, April 30, 1933. At that time, she still had a draining sinus. She was seen at intervals during the ensuing year and was admitted to the hospital 13 months later with a persistent sinus. The distal end of the femur was then operated upon, employing the Orr technic, and the wound healed within six weeks. She has been seen at intervals since and the wound has remained healed.

COMMENT.—A case of Streptococcus osteomyelitis of the femur, with blood stream infection, treated by incision and immobilization of the limb in plaster splints, with Carrel-Dakin treatment of the wound. (For other examples the reader is referred to the case histories of Streptococcus pyarthrosis of the hip joint.)

The results of conservative treatment of five patients with Streptococcus pyarthrosis of the hip joint were most encouraging. In all of them, the joints were first aspirated. In three of these cases plaster hip spicas were applied as well; one case had to have the joint drained two months later, but the other two recovered without operation. In another case, traction was used, following an aspiration, until the twentieth day, when the joint was drained and a plaster hip spica was then applied. The fifth case was an infant of seven months, in which the joint was aspirated but later a drainage was necessary. All of these five patients recovered. One of them could not be followed. The other four obtained functioning hip joints, though in one instance, motion was restricted and in another, there was slight shortening of the limb.

FIVE CASES OF STREPTOCOCCUS PYARTHROSIS OF THE HIP JOINT ILLUSTRATING A MORE CONSERVATIVE FORM OF TREATMENT

Case 1.—Streptococcus Pyarthrosis of the Right Hip Joint: L. L., male, age one, was admitted, December 14, 1935, with a seven-day history of irritability, fever, anorexia and rash. For four days prior to admission he had not moved his right leg. There was swelling of the right hip region and a generalized macular rash. Temperature was 101° F., W.B.C. 14,000, polymorphonuclear leukocytes 52 per cent. The right leg was placed in traction with a one pound weight. For two weeks, the temperature remained around 101° F. The swelling around the right hip joint gradually increased. Then the hip joint was aspirated and 25 cc. of cloudy, straw-colored fluid was obtained. Hemolytic Streptococci were cultured from the fluid. The blood culture at this time was negative. Five days later, the fluid aspirated from the hip joint was considerably thicker in consistency, and incision and drainage was decided upon.

At operation, the joint was drained posteriorly, the wound in the soft parts lightly packed with vaselined gauze, and a plaster hip spica was applied. Eight days following the incision and drainage, the temperature dropped to normal and remained down. The encasement was removed after four weeks. The wound was healed. At this time, there was marked limitation of motion of the hip joint. The patient was discharged, March 6,

1936. One year following discharge from the hospital, both legs measured the same length—37.5 cm. There was very slight loss of extension but no other loss of motion.

COMMENT.—A case of hemolytic pyarthrosis of the hip joint in which drainage was delayed until the exudate became purulent. Treated by means of the Orr method; recovery with little loss of function.

Case 2.—Streptococcus Pyarthrosis of the Right Hip Joint: F. K., female, age 5, was admitted to the Ear, Nose and Throat Service, March 3, 1936, with a two weeks' history of fever and a discharging ear, which followed an attack of measles. On physical examination spasm of the muscles about the right hip was noted. Temperature was 105° F., W.B.C. 13,600, polymorphonuclear leukocytes 60 per cent. The hip joint was aspirated and a small amount of serous fluid was obtained. Culture of this fluid was positive for *Streptococcus haemolyticus*. The right hip was encased in a plaster spica. Following the application of the spica the temperature gradually dropped, during an eight-day period, from a daily level of 105° to around 100° F. The spica was changed at intervals of about two weeks, for eight weeks, when the immobilization was discontinued. At this time a roentgenogram showed "destructive arthritis of the right hip joint characterized by marked osteoporosis of the head and neck of the femur, diminution of the joint space and epiphyseal space between the head and neck." On discharge from the hospital, June 6, 1936, there was marked loss of motion of the hip joint. Examination in the Follow-Up Clinic, one year following discharge, showed 25 per cent loss of extension at the hip joint, 40 per cent loss of flexion, and 10 per cent loss of abduction. There was no shortening of the extremity.

COMMENT.—This case demonstrates the treatment of Streptococcus pyarthrosis of the hip joint by means of aspiration and immobilization.

Case 3.—Streptococcus Pyarthrosis of the Right Hip Joint: P. M., female, age four, was admitted, May 24, 1936, with a four-day history of pain in the right hip and a discharge from the left ear. Two weeks previously, she had had a sore throat and a generalized body rash which subsided after two days' duration. On admission, the child was acutely ill. Temperature 105° F., W.B.C. 12,500, polymorphonuclear leukocytes 80 per cent. She had an acute pharyngitis and a bloody discharge from the left ear. The right hip was held in flexion; there was marked resistance to any motion; a slight amount of swelling was present. A blood culture taken at this time was positive for *Streptococcus haemolyticus*. A small amount of blood-tinged fluid was aspirated from the right hip joint. Culture of this fluid showed *Streptococcus haemolyticus*. A plaster spica was applied, immobilizing the hip joint.

The patient remained critically ill. Temperature level of around 105° F. She was given several small blood transfusions. A week later, the blood culture was still positive for *Streptococcus haemolyticus*, but the child's general condition was improved. The spica was removed at this time and the hip aspirated again. A new plaster spica was applied. Two weeks later, the temperature had dropped, her general condition was improved, and the blood culture was negative for Streptococci. The plaster spica was changed on several occasions, and three months later was removed for good. At that time roentgenograms showed irregularity of the head of the femur, with evidence of some destruction of the femoral head and neck. Since then, there has been no recurrence of the condition in the hip joint. Both legs are approximately the same length. There is slight loss of both abduction and extension of the right hip.

COMMENT.—This patient illustrates the result following an acute streptococcus infection of the hip joint treated by aspiration and immobilization.

Case 4.—Streptococcus Pyarthrosis of the Hip Joint: J. M., male, age seven months, was admitted, January 3, 1933, to the Pediatric Service, with a twenty-four-hour history of cough, vomiting and continuous crying. The baby had had several "crops of boils." He was well nourished, weighing 16 lbs. No abnormal physical findings were noted, except for a reddened pharynx and a furunculosis of the scalp. Temperature was 100° F. A tentative diagnosis of nasopharyngitis was made. The child remained on the Pediatric Service for four and one-half weeks, and apparently recovered from both the furunculosis and the nasopharyngitis. However, at this time the child became irritable, and there was a daily rise of temperature to 103° or 104° F. A diagnosis of osteomyelitis of the upper end of the left femur was made. On aspiration of the left hip joint, a seropurulent exudate was obtained. W.B.C. 21,000 at this time, polymorphonuclear leukocytes 80 per cent. The blood culture was positive for hemolytic Streptococci. Culture from the hip joint was also positive for the same organism. The limb was placed in traction with three pounds' pull. Several small blood transfusions were given. Two other aspirations were done during a period of two and one-half weeks. The temperature remained elevated with daily fluctuations from 101° to 104° F.

At the end of two and one-half weeks, a fluctuant area appeared over the lateral side of the left hip; the hip joint was incised and drained. Thick pus was obtained. Following operation, the leg was again placed in traction. There was a slight drop in the daily temperature curve. One week later, a roentgenogram showed osteomyelitis of the terminal phalanx of the left middle finger. The finger was splinted. For two weeks the condition of the patient remained about the same. Several small transfusions were given. He then developed bilateral, purulent otitis media, which drained spontaneously. Culture from the ears was positive for *Streptococcus haemolyticus*. Following this the temperature gradually dropped to a daily level of around 100° F.; there was a gradual diminution of the amount of drainage from the hip joint; and the weight increased. Seven weeks following the incision and drainage, a plaster spica was applied. This was continued for five months. On discharge from the hospital, February 3, 1934, the wound in the hip region was healed and there was some motion present in the joint. Unfortunately, the patient never returned to the Follow-Up Clinic.

Case 5.—Streptococcus Pyarthrosis of the Right Hip Joint: P. B., female, age 17 months, was admitted, May 7, 1936, with a history of swelling of the right thigh and a perirectal abscess. Two days following admission, the perirectal abscess was drained. Hemolytic Streptococci were cultured from this abscess. One week later, the right hip was aspirated. No pus was obtained. However, the swelling continued and, two weeks later, thick, yellow pus was aspirated from the right hip joint. The joint was then incised and drained. Culture of the pus obtained was positive for hemolytic Streptococci. Following the operation, the extremity was placed in traction for two weeks. A plaster hip spica was then applied. This treatment was continued for two months and, at the end of this time, the wound was healed. One month later, October 21, 1936, the child was discharged.

Six months following discharge, there was only slight limitation of abduction of the hip joint. All other motions were complete. A roentgenogram at this time showed "extensive destruction of the head of the right femur." Two years following discharge, there was no loss of motion at the right hip joint. However, there was 2 cm. shortening of the extremity.

CONCLUSIONS

(1) When death occurs in cases of hematogenous infections of bones or joints, it appears to be due to either a septicemia or a pyemia, the result of the bacteriemia, and is not due to the lesions within the bone or the joint.

(2) Hemic infections due to the Streptococcus behave differently from

those due to the Staphylococcus, as shown by the manifestations of both the bacteriemia and the local lesion.

(3) In consequence, every attempt should be made to recognize the causative organism before treatment is begun.

(4) In treating cases of hematogenous osteomyelitis and pyarthrosis, more attention should be paid to the general condition of the patient than has been done in the past and, before operation is undertaken upon the local lesion, the normal physiologic balance of the body should be established, through the use of intravenous saline and glucose solutions and transfusions.

(5) The local lesions should not be drained by incision until an abscess is formed or frank pus is found to be present, though in cases of pyarthrosis the joint may be aspirated to relieve the tension within its capsule. Lesions due to the Staphylococcus should be drained as soon as the patient's bodily condition warrants it. Those due to the Streptococcus can be drained when a purulent exudate has formed.

(6) In the treatment of both acute osteomyelitis and pyarthrosis, complete immobilization of the limb with infrequent dressings of the wound has proved of benefit—by preventing the spread of infection, by avoiding contamination with secondary organisms and through promotion of healing. Further, because of the relaxation of the surrounding muscles and the assurance it gives the patient of not being hurt, immobilization of the limb has greatly benefited the general morale of the individual. We have often found that the pyrexia rapidly subsides following the application of a plaster encasement.

(7) By employing the procedures which have been recommended, we have shown an improvement in our mortality.

(8) The pyarthroses which have been treated by means of the Orr method have shown far better functional results than those treated by other methods.

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DISCUSSION.—DR. FRANK L. MELENEY (New York): I would just like to speak of one phase of Doctor Beekman's paper, namely, the question of septicemia. In most of these cases, the organism gets in through a portal of entry that is hardly noticeable and then the infection becomes established in

the bone. The original focus of distribution is not the focus from which the septicemia is maintained. The bone focus becomes the major focus and the continuing septicemia is due to distribution of the organisms from the bone focus. So, in cases of osteomyelitis with septicemia, the bone focus is of prime importance. I agree entirely, however, that the septicemia has to be treated first, for if the distribution is not checked, metastatic lesions soon develop in the internal organs—kidneys, liver, spleen or other bones.

In hemolytic Streptococcus osteomyelitis with septicemia, we now have sulfanilamide, which can control the septicemia in most cases without, however, clearing up the bone focus, which later has to be operated upon. For the *Staphylococcus aureus*, on the other hand, drugs are not at present available, although there is some evidence that the new pyridine derivative of sulfanilamide may play a part. During the last few years, potent bacteriophage has been available for the Staphylococcus septicemias and we have found it particularly applicable in the cases with bone or joint involvement. We believe that its action in septicemia is chiefly a clearing of the blood stream and an inhibition of the distribution of the organisms from the bone focus.

Bacteriophage has been in disrepute in times past and I believe that disrepute is due to two things: In the first place, to the too sanguine claims of d'Herelle, its chief exponent; and in the second place, to lack of potent phage. A test for adequate potency has been developed recently in our laboratory. During the last two years, we have been using particularly potent phage and our results, not only in osteomyelitis septicemias but in other cases of Staphylococcus septicemia, have been greatly improved.

Our 36 cases of septicemia have been divided into two groups: namely, the 15 earlier cases, which were treated with phage considered potent because it cleared the culture; and the 21 later cases, in which the phage had been subjected to the double potency test, in other words, phage which not only cleared the culture, but which prevented subsequent growth when the cleared culture was transplanted on a blood agar plate.

Eight out of 36 cases of septicemia had metastases to the bones, which then became distributing foci. Two were in the early group, and both of these died. The other six were in the later group, and all recovered. In one of the early group, and in three of the later group, there was also joint involvement.

Method of Application.—In septicemia, the phage is given intravenously, diluted 1 : 10 in saline, in gradually increasing doses—0.25, 0.5, 1, 2, 3 and 4 cc., at hourly intervals the first day. If there is no reaction, the dose can be more rapidly increased by 5 cc. increments every 12 hours during subsequent days, up to 25 cc. twice a day and continued until there are two sterile blood cultures. If reactions occur, the dose must be increased more slowly. When the bone focus is opened, phage is applied directly to the lesion once or twice a day either on compresses or through Carrel tubes.

Summary of Final Results.—Before October, 1936, our mortality in 15 cases of Staphylococcus septicemia treated with bacteriophage was 76.3 per cent. During the next two years, in 21 cases, the mortality was reduced 28.5 per cent. The mortality for the osteomyelitis cases was reduced from 100 to 0 per cent. A small series, to be sure, but I believe significant. In the phage series as a whole, the mortality was 47 per cent, while in a control series in previous years 81 per cent died. We believe that we will be able to reduce the figure still further if we can get our cases earlier and treat them with a doubly potent phage.

DR. EDWARD T. CROSSAN (Philadelphia): Doctor Beekman and Doctor Sullivan are to be congratulated on their excellent mortality figures and on the end-results they have presented. There is no doubt that the good results are due to the various factors pointed out in their paper. In the first place, adoption of its principles of delay in the operation. Eighty per cent of the deaths in the entire series occurred in those patients operated upon within the first week of the disease. Second, he has called to our attention the importance of differentiation between Streptococcus and Staphylococcus osteomyelitis. The Streptococcus osteomyelitis is a comparatively mild disease, that is, it is not as serious in end-results nor in mortality figures as is the Staphylococcus variety. Third, Doctor Beekman shows that conservative treatment of pyarthrosis is not only time saving and function saving, but also life saving.

DOCTOR BEEKMAN (closing) said that in regard to draining the bone, he has drilled the metaphysis always in fear of damaging the epiphyseal cartilage plate and, in consequence, has found that the drill holes have been two or three inches away from the point at which it was desired to drill. Fortunately, it had not been found necessary to drill in many cases. In three-quarters of the cases of osteomyelitis operated upon, pus has been found beneath the periosteum and when this has been so, Doctor Beekman has gone no farther. If there is no pus found beneath the periosteum, it is usually an indication that the case has been operated upon too early. In such cases Doctor Beekman prefers to make a small trapdoor, but without interfering with the medullary contents of the metaphysis.

Doctor Meleney brought up the question of distribution of bacteria through the blood stream, either from the portal of infection, or from the bone focus. Doctor Beekman said that he had felt more and more, in the last few years, that it is not from the bone focus, but if it is, that affords another reason why one should not operate too soon. For if one does, he will certainly break down the body's defense about that abscess. Doctor Beekman said that, of course, he had tried the old type of phage. It was made from the bacteria of these lesions after they had been draining for some days, weeks or months. Robertson brings out in his observations that the Staphylococcus loses its virulence very rapidly; it is an organism from which antitoxins or good phages should be made in the early periods, while it still retains its virulence. Therefore, if it is possible to reduce Staphylococcus septicemia from 80 to 20 per cent, as Doctor Meleney has apparently been able to do, it is in that direction that one should look in the future for improvement in mortality.

THE TREATMENT OF FRACTURES OF THE NECK OF THE FEMUR BY INTERNAL FIXATION

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THE VALUE of any new surgical procedure cannot be estimated accurately from a small group of cases. This is especially true with respect to fractures of the neck of the femur. Since no one author has reported a very large series of cases, it is essential that each surgeon doing this work should report his results so that a worth while analysis can be made.

Union practically never occurred in these cases prior to 1904, when Whitman proposed his method of treatment. Even since then, the results in this type of fracture have been poorer than the results for any other type of fracture commonly sustained by the human body.

We find, in reviewing the reports of various clinics, that the percentages of union vary from 38 to 65 per cent. In 1929, a committee from the American Orthopedic Association[1] reviewed reports of the leading clinics throughout the country. They found the average of bony union was 50.4 per cent with a mortality of 28.6 per cent. Cleveland and Bosworth[2] recently reported a very interesting résumé of 40 consecutive cases treated by the closed method at St. Luke's Hospital in New York City. The immediate mortality was 14 per cent. Thirty-eight per cent of the total series obtained bony union. Forty-six and one-half per cent of the patients who lived obtained bony union. The average age of those obtaining union was only 59.5 years. The average period in the hospital for those patients was 122½ days. The average cost to the ward patient was $671.50; to the private room patient, $1,000. This did not include special nurses, roentgenologic examinations, operating room charges, or surgeons' fees.

During the last ten years, there has been a concentrated effort by leading surgeons throughout the country to reduce this appalling mortality and percentage of nonunion. From the many reports that are now to be found in the literature, this attempt has been highly successful. Without exception, the method used has been some type of internal fixation.

Any intelligent discussion of this subject must be predicated upon an understanding of certain anatomic and physiologic facts. The head and most of the neck of the femur are intracapsular. The head receives its chief blood supply from blood vessels in the neck of the femur. The remainder comes by way of the ligamentum teres. Therefore, the closer the fracture is to the head, the poorer will be the blood supply to the proximal fragment. This is particularly true if the ligamentum teres has been torn. If one fragment is

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avascular or nearly so, the new bone growth must develop solely from the other fragment and, of necessity, this delays the union. It is probably true that the presence of the joint fluid also helps delay union.

Watson-Jones[3] states that the union of these fractures is governed by the rules of hyperemic decalcification and ischemic recalcification. Motion at the site of the fracture increases the hyperemic decalcification with absorption of the neck and nonunion. Adequate or complete immobilization is not obtained by external fixation. Watson-Jones further states that the degenerative atrophic arthritis which so frequently occurs following a fracture of the neck of the femur takes place because the head of the femur must revascularize and regenerate by invasion of new blood vessels from the distal fragment. The articular cartilage is less resistant and undergoes degenerative changes when deprived of blood for any length of time and when exposed to the trauma of early weight-bearing. This unfortunate phenomenon was demonstrated in one of our early cases of subcapital fracture, in which we permitted weight-bearing from the first although union occurred at the site of the fracture.

Fractures of the neck of the femur must be divided into two groups. The first group includes those occurring in the neck proper or intracapsular fractures. This is the type in which delayed or nonunion occurs. The second group embraces trochanteric or extracapsular fractures, which practically always heal. These cases have a rich blood supply from both ends of the fragments.

In 1931, Smith-Petersen[4] perfected his method of treating fractures of the neck of the femur by internal fixation with a specially designed three-flanged nail. Since that time, numerous and sundry gadgets have been devised to obtain similar results. The same basic principle underlies all of the various inventions, that is an attempt to obtain absolute and continued immobilization and a satisfactory anatomic reduction. When these two prerequisites are fulfilled, the fracture should heal as well as any other in the human body.

Originally, the internal nailing operation was confined to the intracapsular fractures. In recent years many more operators are using the nailing procedure for trochanteric fractures, not primarily to obtain union, but because of the markedly shortened period of hospitalization, the absence of ankylosed knees and ankles, and the absence of the long chain of potential complications which may occur to an aged individual who is kept bedfast for a period of three or four months.

These facts were demonstrated very clearly to us by two male patients who were admitted to the hospital with identical fractures on the same day. They were both in good health and of approximately the same age. One was a farmer and the other a business man. The farmer was treated by the usual methods which required his being in bed in the hospital for a period of three months, followed by an additional period of three weeks in which he was becoming ambulatory on crutches. At one time, while he was in the hospital, the skin was broken by skin traction requiring some special surgical

care. At another time, he developed an atelectasis and was quite sick for several days. He had a great deal of difficulty in sleeping and was pretty well worn out when his period of immobilization was over. Added to his disability was a stiff knee and ankle with the usual swelling of the extremity when on his feet. Bony union occurred at the end of three months with the fragments in good position. It was nine months from the time of his fracture before he was really back to normal and able to carry out his duties on the farm.

The other patient, the business man, had heard about internal fixation and requested that we carry out this procedure in his case. His operation was not attended with any difficulties. He was in a wheel chair within a week and was able to handle himself well on crutches at the end of two weeks at which time he was discharged from the hospital. He was back in his office at the end of three or four weeks from the time of his accident. This man continued to look after his business affairs during the entire period of his convalescence. At the end of three months he was in excellent physical condition and had maintained his normal weight. There was no stiffness of the knee or ankle and no swelling of the lower extremity. He obtained union in three months as did the man who was kept hospitalized.

Comparing these two cases, it is obvious that the operative method is the procedure of choice. The first man was hospitalized for almost four months; he was faced with a large hospital bill; was considerably under par from his experiences in the hospital; and it was nine months before he could resume his normal activities. The second man was in the hospital three weeks and was away from his duties at his office for only one month. Since that time we have operated upon all trochanteric fractures routinely.

Trochanteric fractures require the observation of certain important details. We consider the Moore nails best adapted to this work because of the lessened danger of fracturing the remaining shaft of the femur. Furthermore, the nails must be inserted at a slightly lower level than would be desirable for an intracapsular fracture. This is done to obtain a more solid attachment for the nails in the distal fragment. There is less likelihood of having the nails bend or pull out. There is also less shearing force on the nails from weight or muscle pull. In many cases the fracture extends through the shaft to the outer side of the trochanter so that in order to get into the distal fragment one may have to insert the nail as much as two or two and one-quarter inches below the base of the trochanter. We have found it advisable to drill the openings for the Moore nails with an ordinary bone drill which is slightly smaller than the nail itself. This procedure greatly facilitates the insertion of the nails.

Preoperative Care.—When the patient comes to the hospital he is placed in an ordinary bed, and a Buck's extension is applied to the broken limb with about ten pounds of traction. Sand bags are placed on either side to prevent movement and external rotation. Small doses of morphine are given for pain, intravenous glucose and blood transfusions are given until the patient's blood

count is normal, and his normal water balance established. The operative procedure is not attempted until the patient is eating normally and taking sufficient fluids by mouth for his normal requirements. In other words, the patient must be returned, as nearly as possible, to his normal condition prior to the accident before the operation is attempted. In our experience this will require from seven to ten days, and in some cases even a few days longer. If immediate operation is carried out, unquestionably there will be an unnecessarily high mortality credited to the procedure.

Operative Technic.—The skin is prepared the night before the operation and sterile dressings applied. A mild sedative is administered the morning of the operation. The patient is transported to the operating room in his bed. A low spinal anesthesia is administered. He is then lifted to the operating table and the fracture reduced by the Leadbetter[5] technic. Both feet are attached to the foot pieces of the Albee table. Both legs are brought out to about 30° abduction and the affected limb placed in full internal rotation. Anteroposterior and lateral roentgenograms are taken with a portable unit. While these are being developed, the patient is draped and a lateral incision is made which exposes the trochanter and the proximal end of the shaft. If the roentgenograms show the fragments are in good position (which is usually the case), we are ready to proceed with the first part of the operation. We do not feel that any elaborate apparatus is necessary for finding the head of the bone. A towel clamp is placed over Poupart's ligament midway between the symphysis pubis and the anterior superior spine. This will be approximately over the head of the femur.

In those cases in which the Smith-Petersen nail is used, four or five Kirschner wires are drilled into the head of the femur. These enter at various levels. This is done for two purposes: First, to make new openings into the head of the femur for additional blood supply; and second, we desire to pick the wire that is best situated for the insertion of our nail. After this has been accomplished, a sterile sheet is placed over the patient and operative field. Roentgenograms are taken again in both anteroposterior and lateral views. Needless to say, the close cooperation of the personnel of the Roentgenologic Department is highly desirable. The best wire is chosen and the others extracted, so that they will not interfere with the entrance of the nail. On a few occasions we have had difficulty with the nail wandering as it was threaded over the guide wire. This results in a bent wire which offers considerable difficulty on extraction. To combat this, we simply insert the nail beside the wire. Occasionally, difficulty will be encountered by the projecting portion of the guide wire being deflected by the hammer. To correct this, we drill an additional wire about one-half inch away but on the same plane and use this as an additional guide.

The surgeon who is attempting this operation for the first time should be warned that the roentgenograms magnify the actual distance from the shaft to the head of the femur. There are many unique methods devised to estimate this discrepancy. In our experience, the actual distance is about

80 per cent of the measurement on the film. Probably the easiest way to calculate this is to estimate it from the wire which is being used as a guide. The length of the wire is known. We measure the amount that protrudes and then knowing the length of the remainder estimate the length of nail necessary. If the nail enters the acetabulum, it should be pulled back into the head to avoid permanent damage to the joint.

After the nail is inserted, the Kirschner wire is extracted and the nail driven in tight so that the fragments are impacted. A sterile sheet is again thrown over the patient and further roentgenograms taken so that we can be certain that our nail is in proper position and the fracture properly reduced. As soon as this is ascertained, the wound is closed.

As an operator gains experience, the procedure becomes quite simple. With the foot in full internal rotation the neck of the femur is in the horizontal plane. A towel clamp is placed midway between the anterior superior spine and the symphysis pubis. This gives the approximate location of the head. If the nail is started an inch to one and one-half inches below the base of the trochanter at an angle of 45° with the shaft, directing the point toward the towel clamp and on a horizontal plane, the nail will enter the head in the majority of cases.

We have found in an occasional case in which it was necessary to expose the joint and the fracture line, that the following incision gives an excellent exposure:

The usual lateral incision is extended from the trochanter for a distance of about three inches upwards and in front of the anterior superior spine of the ilium. The muscle fibers attached to the anterior base of the trochanter and the upper two inches of the shaft are cut and retracted. The capsule then comes into view. A short transverse incision is made in the base of this. A second one is made from the base to the acetabulum in the longitudinal plane. The whole neck, fracture line and head of the femur will then be exposed. The fracture can then be accurately reduced and fixed with the nail by direct vision.

Precautions to Avoid Shock.—The observation of a few simple rules should obviate practically all symptoms of shock during the operative procedure. Because of the necessity of considerable delay in the taking and developing of the roentgenograms, the operation must, of necessity, consume in the neighborhood of one hour's time. A general anesthesia of this duration in an aged individual is not desirable. Local anesthesia, even in the best hands, will be accompanied by a certain amount of pain. In our experience a low spinal anesthesia is the one of choice. It is not painful to administer, the anesthesia is complete, and can be used over a prolonged period of time without adding to the morbidity. Intravenous 5 per cent glucose is started immediately after the patient is placed upon the operating table. The patient is wrapped in warm blankets not only on the trunk but on the unaffected limb and from the knee down on the affected limb. Over the blankets are placed hot water bottles which are retained in position by bandages. In

this way we can conserve the patient's body heat, the dissipation of which we feel contributes considerably to the production of shock. If there is a marked fall in blood pressure, adrenalin or epinephrine is given hypodermatically. Considerable care is exercised to insure the loss of as little blood as possible. The wound is never left exposed during the waiting periods for the developing of the roentgenograms, hot saline packs being placed in the depths of the wound. It has been our experience that if these precautions are taken, there will be practically no shock whatever regardless of the patient's age. In the majority of cases the patient will sleep peacefully through the operation and will have to be awakened to be advised that the operation has been completed.

Postoperative Care.—At the termination of the operation, the patient is placed in a warm bed with a sand bag on either side of the leg or with a short board nailed to a shoe or bedroom slipper to hold the foot erect and prevent external rotation. He is encouraged to take water and food as though nothing had happened. The next day the patient is propped up in a sitting position in bed. In the next day or two he is placed in a wheel chair. As soon after this as he is strong enough he is given crutches and walking is started. We find that in the average case this will be a week or ten days from the time of the operation. The patient is then ready to be discharged from the hospital unless there is some other complication requiring further hospitalization.

The Question of Weight-Bearing.—The first three or four of our early cases were permitted weight-bearing before union had occurred. One of these cases had some degenerative arthritis around the head. Another case was one in which the patient wore a plaster encasement for three months because the pin extended into the acetabulum. After the second pin was placed in the hip she was permitted weight-bearing. This may have had something to do with the nonunion. Since the first few cases, it has been our rule never to allow weight-bearing until solid union can be demonstrated roentgenologically. By this we mean that bony trabeculations must be seen traversing the fracture line. This usually requires from four months to a year. We believe that this is one of the principal causes for nonunion and arthritis. The patient is permitted normal motion of the knee and ankle within the first week after the operation. Full range of motion in the hip is not encouraged for about six weeks. It is probable that the majority of the patients move the extremity through the normal range of motion within the first few weeks. Apparently it does no harm as the flanged nail prevents rotation of the head on the neck.

The Use of External Fixation or Plaster Spicas.—We use absolutely no type of external fixation plaster spicas in the intracapsular fractures. Apparently, the pin gives all the support that is necessary. In trochanteric fractures, unless the fracture line is close to the base of the neck, we feel that it is possibly a little safer to use a short hip spica for about six weeks because of the danger of the head of the nail or Moore pins being pulled through the thin shaft. In our series, there was only one exception to this rule. This was in a man, age 83, who left the hospital ten days from the

time of operation with the promise that he would do nothing more than sit in a wheel chair for a period of six to eight weeks. His family physician wrote me about eight weeks later stating that the patient had been walking without a cane or a crutch from the fourth week. At the end of five months, he fell down a long flight of cellar steps, badly bruising himself. Roentgenograms taken of the hip revealed it in perfect position and perfectly healed. Apparently the wires had not even bent with his walking at the end of a month's time.

Indications for Operation.—We feel that we are justified in operating upon any patient whom we believe will live a month or six weeks from the time of operation, if for no other reason than to relieve him of his pain. We believe that any patient who has survived the original shock of his injury and has improved to the point that he is taking fluids freely and is eating normally, will survive the operation without mortality, barring unpredictable accidents or complications. In our series we operated upon all cases that we saw, the ages varying from 39 to 95.

Advantages of Internal Fixation.—In reviewing the literature, we found that the mortality for any of the closed methods varied from 15 to 40 per cent. The average mortality for internal fixation was less than 10 per cent. The highest percentage of union reported by the closed method was 65 per cent, the majority being 50 per cent or less. The average percentage of union by internal fixation was above 80 with many over 90. The period of hospitalization is very materially decreased, thereby markedly decreasing the cost of hospitalization. When the closed method is used, a large percentage of aged patients develop senile dementia or other cerebral changes. There is much less danger of this complication when early discharge from the hospital is made possible by the use of internal fixation. A very important factor is the complete cessation of pain following the operation.

The Question of Removal of the Nails After Union Has Occurred.—We feel that after union occurs in young individuals, the nail should be removed. To date, we have removed only two, and in both cases the nails still fitted snugly in their grooves. Roentgenologically, no changes could be seen, and both had been in over a year. In the older individuals, particularly those past 75, unless the nail gives trouble, we do not think it is necessary to remove it. With the development of Venable or "vitallium" nails, which theoretically cause no electrolysis or change in the bone, it may be unnecessary to remove them at any age. We shall be able to reach a definite conclusion only after watching these cases over a long period of time.

IMPORTANT POINTS IN THE TREATMENT OF FRACTURE OF THE NECK OF THE FEMUR BY INTERNAL FIXATION

(1) Operation should not be undertaken for at least seven to ten days after the time of the accident or until normal physiologic functions have been restored.

(2) A minimum degree of anesthesia should be used. We prefer a low spinal.

(3) The fracture is reduced by the Leadbetter technic.

(4) Intravenous glucose should be administered during the operation and the patient wrapped with blankets and hot water bags to prevent loss of body heat.

(5) The nail should be placed one inch below the base of the trochanter and enter well into the head.

(6) Both lateral and anteroposterior roentgenograms should be taken during and after the operation.

(7) The patient should be encouraged to be ambulatory on crutches as soon as possible.

(8) There should be absolutely no weight-bearing until solid union is demonstrated roentgenologically.

APPRAISAL OF THIS SERIES OF 25 CASES

The age incidence varied from 39 to 95, the majority of the patients being past the age of 70. Seventeen were intracapsular fractures and eight trochanteric. The first case was operated in January, 1936. All cases have been followed since the time of operation. The end-results are known. All of the cases of trochanteric fractures have healed. Of the intracapsular fractures, two patients have died, one from hemiplegia five months after the operation. Until the time of her death she was getting along very nicely on crutches and was apparently obtaining union. The second died six months after operation from cardiovascular disease. He had no pain, had normal range of motion, but had been bedridden for two months before his death because of his terminal diseases. There has been one death in the trochanteric fractures. This patient died of apoplexy five months after operation. Union was complete, as shown roentgenologically six weeks before her death.

FIG. 1.—Case 8: After the first operation showing the rotation of the head.

This, then, leaves 15 cases of intracapsular fracture which have lived. Two of the 15 cases have not had satisfactory results. The first developed nonunion and sequestration of the head. This was the case in which the nail entered the acetabulum. The patient was immobilized in a plaster spica for three months, at which time the nail was removed and another shorter nail inserted. Weight-bearing was permitted at this time. The neck has gradually absorbed, the nail is eroding up through the head into the acetabulum. The patient is still walking around but has some pain. Further surgical treatment will be necessary.

The second case was a subcapital fracture with a rather marked comminution of the neck with pieces of loose bone between the two main frag-

ments. At the original operation it was impossible to obtain a satisfactory reduction. At the time the operation was completed, an anteroposterior view showed the pin in good position, but the lateral was not clear. The wound was closed and a roentgenogram the next day revealed the fact that the pin caught only a little of the posterior portion of the head and that the head

FIG. 2.—Case 8: After the second operation.

FIG. 3.—Case 8: The neck is mostly absorbed.

FIG. 4.—Case 8: After the Colonna operation.

FIG. 5.—Case 2: Subcervical fracture healed.

FIG. 6.—Case 9: Subcapital fracture healed.

FIG. 7.—Case 15: Subcapital fracture healed.

itself had rotated. Unquestionably, the ligamentum teres was torn in this case. Ten days later a second operation was performed, with wide exposure of the joint, and even then a nail could not be satisfactorily placed so as to reduce the fragments, there being a short distance of gaping between the two. We believe this would have been an ideal case for a bone graft. Several months later the patient developed an aseptic inguinal abscess which was

drained. Still later, a septic infection developed in the sinus tract which extended into the joint. The neck was gradually absorbed and the head became a sequestrum. This necessitated the removal of the nail and the sequestrated head, with the performance of a Colonna reconstruction operation to obtain a stable hip. The patient was kept in a plaster spica for a period of four weeks. At the present time he has about normal flexion and extension, but no abduction. There is three-fourths of an inch shortening. There is practically no pain. He has an excellent result.

Reviewing these cases, I believe that Case 1, in which the nail entered the acetabulum, was an example of a severed ligamentum teres. Case 13, in which we used a bone graft, had a severed ligamentum teres. Also, in Case 8, described in the preceding paragraph, the ligamentum teres was severed. In a fourth case, recently operated upon but not included in this series, the ligamentum teres was severed. All of these had subcapital fractures. They accounted for the two cases of nonunion in this series, and unquestionably would have accounted for the third if a bone graft had not been used. The patient just recently operated upon had a bone graft used for fixation. A surgeon should suspect that the ligamentum teres is severed in any case of subcapital fracture in which the head tends to rotate when a pin is introduced. While we have only had this experience in a few cases, I believe that it is wise to use a bone graft instead of metal fixation when there is a suspicion that the ligamentum teres is severed.

Summarizing the results obtained in the 25 cases of this series, we note that there have been eight trochanteric and 17 intracapsular fractures. One of the trochanteric fractures died five months after operation, but union had already occurred. Two of the intracapsular fractures died after a five-month period but before union had occurred. Two cases had nonunion with a dead head. The remaining 13 have solid bony union. All of the trochanteric fractures obtained union. Since we are not attempting to improve our results as far as union is concerned in the trochanteric fractures, we will only consider the intracapsular fractures. Out of the 17 intracapsular fractures, solid bony union was obtained in 76 per cent of all the cases. If the two patients who died after a five-month period are eliminated, bony union occurred in 86.6 per cent of the remainder. There were no cases of operative infection. There was one case in which an aseptic abscess developed several months after the operation which, in turn, was infected through the sinus tract. There was no operative mortality. The closest death to the time of operation was five months. Of the 25 cases, 22 are still living.

Statistics of Other Authors.—Watson-Jones[3] reports a series of 64 cases. His first series was composed of 29 cases with 79 per cent bony union. The next group was composed of 35 cases with a 91 per cent bony union. The total operative mortality was 6 per cent.

Willis Campbell[6] reports a series of 35 cases, 19 of which had been under observation long enough to determine the end-results. All of these obtained bony union. Only two of these showed any late changes in the head.

TABLE I

SYNOPSIS OF 25 FRACTURES OF THE NECK OF THE FEMUR TREATED BY INTERNAL FIXATION

Sex	Age	Date of Operation	Period of Hospitalization	Type of Fracture	Type of Fixation	Time Required for Bony Union	End-Results
1. F.	52	1-13-36	13 days	Subcapital	Smith-Petersen nail	Nonunion	Walks with nail giving support. Some shortening and pain
2. F.	78	2- 6-36	32 days	Subcervical	Smith-Petersen nail	8 mos.	No pain or shortening
3. F.	76	3- 4-36	22 days	Subcapital	Smith-Petersen nail	6 mos.	Slight shortening and some arthritis. Very little pain
4. F.	82	6-16-36	50 days	Subcapital	Smith-Petersen nail	Died 5 mos. later with stroke. Had been walking on crutches. Recent roentgenograms had not been taken to determine amount of union. Had no symptoms	
5. M.	81	8-10-36	24 days	Midcervical	Smith-Petersen nail	7 mos.	No pain or shortening
6. F.	79	9-29-36	45 days	Subcapital, comminuted	Smith-Petersen nail	6 mos.	No pain or shortening
7. M.	43	2- 4-37	45 days	Subcapital	Smith-Petersen nail	4 mos.	No pain or shortening
8. M.	30	2-26-37	60 days	Subcapital	Smith-Petersen nail	Nonunion. Developed aseptic abscess several months after operation. Infection later developed in sinus tract. Colonna operation eventually performed, with good result	
9. F.	40	3-23-37	40 days	Subcapital	Smith-Petersen nail	7 mos.	No pain or shortening
10. F.	68	5-27-37	54 days	Subcapital	Smith-Petersen nail	14 mos.	No pain or shortening
11. M.	80	6-23-37	26 days	Subcapital	Smith-Petersen nail	Died 5 mos. later, with cardiorenal disease. Results unknown	
12. M.	58	8-27-37	14 days	Intertrochanteric	Smith-Petersen nail	3 mos.	No pain or shortening
13. F.	54	10-20-37	22 days	Subcapital, comminuted	Bone graft	6 mos.	No shortening
14. M.	74	12- 6-37	60 days	Intertrochanteric	Smith-Petersen nail	3 mos.	No pain or shortening
15. F.	72	12-13-37	30 days	Subcapital	Smith-Petersen nail	5 mos.	No pain or shortening
16. F.	95	1-12-38	18 days	Trochanteric	Steel nails	4 mos.	Slight bowing; very little pain. Died 5 mos. after operation with stroke
17. F.	60	1-17-38	20 days	Trochanteric	Moore nails	7 mos.	No pain or shortening
18. M.	52	1-24-38	6 days	Trochanteric	Moore nails	6 mos.	This fracture was about 3 mos. old when seen with no union. Slight shortening. Now solid union
19. F.	75	2- 2-38	16 days	Subcapital	Smith-Petersen nail	5 mos.	No pain or shortening
20. F.	78	3- 7-38	26 days	Midcervical	Smith-Petersen nail	4 mos.	No pain or shortening
21. M.	83	4- 2-38	12 days	Trochanteric	Moore nails	4 mos.	No pain or shortening
22. M.	45	5-28-38	12 days	Trochanteric	Moore nails	3 mos.	No pain or shortening
23. F.	60	6- 9-38	11 days	Midcervical	Smith-Petersen nail	4 mos.	No pain or shortening
24. F.	82	7- 5-38	23 days	Subcervical	Smith-Petersen nail	3 mos.	No pain or shortening
25. F.	42	9-28-38	16 days	Trochanteric	Moore nails	Patient is walking on crutches. Union is practically complete	

James Dickson[7] reports a series of 18 cases. Twelve of these cases had been operated upon long enough to see end-results, all of which obtained bony union. The other six were healing satisfactorily.

Henderson[8] reports a series of 14 patients with an 86 per cent bony union and no mortalities.

Moore[9] reports 25 cases of intracapsular fractures in which sufficient time had elapsed to make a definite end-result study. Only one failed to obtain bony union. In other words, there was a 96 per cent successful end-result. There were no deaths attributable to the operation.

R. I. Harris[10] reports 50 cases of intracapsular fracture of the neck of the femur treated by internal fixation, the Smith-Petersen nail being used in all of the patients. Bony union was obtained in 76 per cent of the cases. Five patients died, giving a mortality of 10 per cent. There was an 80 per cent bony union in the surviving patients.

Plummer[11] reported 33 cases of intracapsular fracture. Only two patients died within the ten-day postoperative period. While he does not give a percentage of bony union, one gathers from his report that his experiences have been highly successful.

CONCLUSIONS

(1) A review of the literature reveals that the treatment of fractures of the neck of the femur by closed methods does not give satisfactory results.

(2) The use of internal fixation for fractures of the neck of the femur is a safe procedure. It decreases the financial strain on the patient, lessens the period of hospitalization, lowers the mortality and very definitely improves the end-results.

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BRIEF COMMUNICATIONS AND CASE REPORTS

JACKSON–GALLAGHER DEPTH GAUGE

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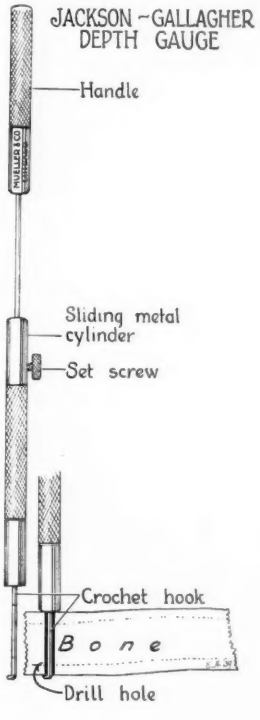
IN the open reduction and plating of fractures of the shaft of a long bone transfixion screws are often required; especially is this true when the shaft of the femur is plated. To obtain the correct length of the screw to be used, *i.e.*, one that will contact and fix both cortices of the bone, it has been customary to use a micrometer or caliper. The same applies wherever transfixion screws are used in bone work. This is a cumbersome and tedious procedure and due to the variable thicknesses of the bone and the different angles at which the screws are inserted, is not an accurate method.



Surgeons are often surprised to find on examining postoperative roentgenograms that the screws used were frequently either too long or too short. To obviate this difficulty we have devised a simple instrument that we term a depth gauge.

The accompanying illustration is almost self-explanatory. The instrument consists of a shaft of stiff wire with a small crochet hook on the lower end. On the shaft is a sliding metal cylinder with a set screw.

To determine the exact length of the screw to be used, the wire is passed completely through the drilled hole in the bone and then pulled back until the crochet hook lodges against the opposite cortex. The sleeve is now dropped against the bone and the set screw locked. The instrument is then withdrawn and the distance from the end of the sleeve to the crochet hook gives the exact length of screw required for that particular hole. When using a plate one must allow for its thickness. In using self-tapping screws it is well to allow for the tapered end of the screw.

We wish to express our appreciation to Mr. Ted Larson of the V. Mueller Company of Chicago for his cooperation in making this instrument.

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WATERMELON SEED IN GALLBLADDER

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THE NUMBER of recorded cases of foreign bodies in the gallbladder is comparatively small. Toland,[1] in 1933, reported a case of common duct obstruction which, at operation, revealed a bolus of cotton gauze impregnated with bile, bile salts and fibrin. The cotton gauze had been left in the gallbladder at a former operation by a different surgeon. Toland reviews the literature and lists the types of foreign bodies that have been reported to have been found in the biliary tract, including such objects as a rifle bullet, seeds, worms, steel needles, piece of wire, swabs, rubber drain tube and handle of a spoon.

The case herewith reported is from a cadaver in the Anatomic Laboratory and the foreign body was discovered by two medical students, J. S. Arnold and J. H. McVicker. The department records on this cadaver are very meager. The body was sent to the Anatomic Board from a private mortuary and it has not been possible to obtain any information regarding either the medical diagnosis or treatment before death. The death certificate gives the following information:

Case Report.—Negro, female, age 65. Died August 28, 1936. *Cause of Death:* "Chronic myocarditis, senility."

Autopsy Findings.—Dissection of body was begun, September 26, 1938. The cadaver was exceedingly obese. The skin was intact on all parts of the body with the exception of the thigh where incision had been made for embalming. There was no scar indicating any surgical procedure during life. On opening the gallbladder, a well preserved watermelon seed was found in it together with some five or six gallstones of various sizes. There were no adhesions of the gallbladder to any part of the stomach or intestines, indicating any possible previous ulcer. The common bile duct measured 12 Mm. in diameter in the flattened state. The ampulla of Vater was very prominent. It extended into the cavity of the duodenum as a conical papilla of about 10 to 12 Mm. in height (it was not measured). Two prominent folds of mucous membrane extended from the summit of the ampulla distally. The gallstones were examined chemically by Mr. McVicker and were found to consist of cholesterol and ergosterol.

Discussion.—The significance of the possibility of foreign bodies migrating from the duodenum to the gallbladder, in the etiology of gallbladder disease, is immediately apparent. It has generally been held that foreign bodies do not pass from the duodenum to the gallbladder. Toland says: "It is logical to assume needles and other sharp objects that have been swallowed and reached the pylorus might migrate by direct contiguity into the gallbladder. The curious circumstances that lead to such migration are difficult to visualize. Inanimate foreign bodies in the gallbladder can hardly be explained on the basis of retrograde migration from the duodenum through the ampulla of

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Vater, but the motile round worm could easily reach the gallbladder by this route."

The importance of ascending biliary infection in the etiology of gallbladder infection has been recognized in standard text-books. Babcock,[2] in his Text-Book of Surgery, says: "The bacteria enter the ampulla of Vater, passing through the common and cystic ducts into the gallbladder. This process may be aided by the reverse currents described by Bond, who found that carmin introduced into the rectum would ascend and pass out through a gallbladder fistula."

The actual passage of duodenal contents into the biliary system has been recorded by a number of authors. Such a reflux of duodenal contents, apparently, was first noted, clinically, by Codman,[3] in 1908. McArthur,[4] in 1923, reported a case of reflux of barium into the common bile duct. Davis,[5] in 1929, reported four cases of duodenal reflux. Walters and Marshall,[6] in 1930, reported four cases in which pancreatic enzymes were recovered from drainage tubes in the biliary system. They also found that methylene blue given by mouth appeared in the drainage material. Bernard,[7] in 1934, reported eight cases of duodenal reflux. This occurred in patients after choledochoduodenostomy, choledochotomy and cholecystectomy. The reflux was demonstrated roentgenologically after a barium meal. In some cases the barium extended into the smaller radicals of the hepatic ducts.

Reflux of duodenal contents has also been demonstrated by animal experimentation. Higgins and Mann,[8] in 1926, working on the bile expulsion mechanism in guinea-pigs, reported that portions of test meals injected into the duodenum pass directly into the common bile duct. The following year, Burget and Brocklehurst[9] were not able to force duodenal contents into the intact ampulla of the guinea-pig. These authors reinvestigated the anatomy of the biliary tract in the guinea-pig and describe a "contractile ampulla which opens into the duodenum." This structure is apparently peculiar to the guinea-pig.

More recently, Auer and Seager[10] have investigated the problem of reflux of duodenal contents into the biliary system of the guinea-pig. In 23 out of 26 guinea-pigs, they were successful in forcing air or dilute India ink into the gallbladder and biliary passages. The effective duodenal pressures necessary for duodenal reflux ranged between 10 and 20 Mm. Hg.

Another type of reflux into the biliary system has been investigated, especially by Wolfer.[11, 12] In 1931, he reported on the results of experiments of introducing pancreatic juice into the gallbladder of dogs. In 1937, he reported a case of pancreatic juice reflux into the gallbladder of a patient and reviewed the literature on this type of reflux into the biliary system. As stated by Wolfer, this type of reflux is perhaps dependent upon total or partial obstruction of the ampulla of Vater and especially in such cases where the pancreatic duct and the common bile duct join to have a common opening into the duodenum.

A few references in the literature to "duodenal reflux" deal with duodenal regurgitation into the stomach. It is suggested that the term "duodenal reflux" be limited to a passage of duodenal contents into the biliary system.

There seems to be no other explanation for the presence of the watermelon seed in the gallbladder than that it passed by way of the ampulla of Vater and the common duct. From the appearance of the seed, together with the season and the observation of a great quantity of seeds in the large intestine, its sojourn in the gallbladder had probably been of only a few days' duration before death.

In the list of foreign bodies given by Toland, the majority of the foreign bodies represent accidental inclusions resulting from surgical procedures. Mertens[13] (1898) reported two instances of worms (Ascaris lumbricoides) which had undoubtedly entered by way of the ampulla of Vater. Although various authors mention cherry stones and seeds as having been found in the gallbladder, I have been unable to locate the original reports of any such observations. Mertens and Deaver,[14] referred to by Toland, make no mention of seeds in the gallbladder.

The presence of seeds in the gallbladder could hardly be accounted for by any other route than the ampulla of Vater and the common duct, unless, as has been suggested, by a rupture of an ulcer of the stomach which was adherent to the gallbladder. As stated above, there was no evidence of any such pathology in the case here reported.

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TUBERCULOSIS OF THE LATERAL LUMBAR VERTEBRAL MASS

OPERATIVE CURE

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TUBERCULOUS OSTEOMYELITIS of the lateral lumbar vertebral mass of any of the vertebra without simultaneous involvement of the corresponding body has, as far as we can ascertain, not yet been reported in the literature.

The following case was encountered while the patient was under treatment for tuberculous osteomyelitis of the thoracic wall and for tuberculous lymphadenitis of the cervical region (postoperative). We believe this case is one of unusual interest in that the site of the spinal infection is a rare one, and also that the lateral portions of the ribs are not frequently the source of abscess of the chest wall (Alexander[1], and Carr and Alexander[2]).

Case Report.—C. D., Filipino, male, age 34, was admitted to the New Jersey Sanatorium, Glen Gardner, N. J., July 20, 1936, with a diagnosis of minimal pulmonary tuberculosis. The lesion was discovered during a routine examination of food handlers. He had had a right cervical adenectomy performed in August, 1935, for ulcerative adenitis. The wound had failed to heal completely. He was asymptomatic except for a 24-pound weight-loss since November, 1935 (eight months). Incidentally, he gave no history relative to the draining sinuses located in the axillary region over approximately the eighth rib, which were discovered during physical examination. Inquiry, however, showed that the onset had been gradual, commencing about November, 1935.

Physical Examination.—The patient appeared chronically ill, and decidedly underweight. There was a series of draining sinuses extending from about 4 cm. below the mastoid process on the right to approximately 6 cm. above the clavicle, and 2 cm. posteriorly from the lateral border of the sternocleidomastoid muscle. These had the appearance of tuberculous sinuses. There was also a cluster, one large and several small, of sinuses located over the seventh and eighth intercostal spaces and the eighth rib in the axillary region on the right side. The surrounding area was raised, but no tenderness could be elicited. Cheesy material was expressed in considerable quantities upon moderate pressure. The impression was gained that more than one rib was involved. The regional lymph nodes were considerably enlarged but not tender. The examination of heart, lungs, abdomen, *etc.*, was negative.

Laboratory Data.—Sputum and urine were negative for acid-fast bacilli. Blood and urine were normal. Roentgenologic examination of the chest showed an old fibrous, minimal lesion in the apex of the left lung as well as destruction of the eighth rib in the axillary line with an accompanying soft tissue swelling and a localized area of density

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resembling fluid, protruding into the pleural space immediately subjacent to the involved rib.

The patient was first placed upon routine sanatorium regimen for a period of about two weeks. He was then referred to the Surgical Service. The complete operation was divided into two stages because the process was far more extensive than appeared upon first examination. Careful probing of the sinuses revealed ribs 6, 7, 8, and 9 to be involved.

Operation.—August 5, 1936: The principles employed in resecting the involved tissue and bone followed those described by Alexander, namely: "Radical excision of every bit of infected tissue and of any normal cartilage that has been cut into." The final closure was not complete, necessitating the leaving of an area which granulated in and was ultimately closed by skin graft. The subsequent postoperative course was essentially uneventful, even though the process had eroded through the parietal pleura, causing a local accumulation of fluid. Postoperative aspirations were necessary but empyema did not develop.

Subsequent Course.—An uneventful convalescence, with satisfactory clinical improvement and weight-gain, marked the patient's course until October 21, 1936, when a mass, approximately the size of an orange, suddenly appeared over the right iliac region. On examination, this mass proved to be definitely fluctuant and without associated pain, tenderness, or increase in local heat. Aspiration was performed and a quantity of thick pus obtained. Bacteriologic study of the specimen was reported as negative for all organisms.

Intravenous pyelograms and anteroposterior and lateral roentgenographic projections of the spine were made. The former showed no evidence of a destructive lesion of either kidney. The latter, however, revealed a destructive process involving the lateral third lumbar vertebral mass (Figs. 1 and 2). The process was one of bone destruction, practically without bone formation, and, therefore, was concluded to be tuberculous osteomyelitis. It was also observed that, in the anteroposterior projection, there was an obliteration of the lateral border of the silhouette of the psoas muscle, while on the contralateral side there was no such interference with the normal psoas shadow. Because of the age of the patient (approximately 34 years at the time of onset), and the fact that, at operation, a fair-sized sequestrum was removed, we are inclined to believe this process was of comparatively recent origin and did not date back to the time of adolescence before body growth was complete.

We mention this specifically, because the lateral projection shows that the destructive process has involved the side of the body of the vertebra as well as the transverse process. In this view, one may also note a decrease in the density of the pedicle. Embryologically, then, the total area involved corresponds to the lateral mass of the vertebra except its posterior portion, and, therefore, we were dealing with a tuberculous osteomyelitis of the lateral mass of the third lumbar vertebra and not merely of the transverse process itself. The negative bacteriologic reports on pus obtained from the cold abscess, and the presence of preexisting tuberculous lesions elsewhere, were taken as presumptive evidence substantiating our diagnosis. Pus accumulated quite rapidly in the abscess pocket and eventually broke through a needle track which had failed to heal even though it was not dependently placed and had passed through healthy tissue before entering the abscess cavity.

It was not felt that we were dealing with a true Pott's disease, but rather with a condition quite comparable to a tuberculous osteomyelitis of the rib. In view of this, open operation was decided upon.

Second Operation.—November 18, 1936: Under a 5 per cent procaine local anesthesia, an 8 to 9 cm. longitudinal incision was made centering over the involved transverse process and placed between the junction of the outer one-third and inner two-thirds of the erector spinae muscles. Blunt dissection was used as far as possible throughout the procedure. This brought a large abscess directly into the operative field, and about four to five ounces of thick pus was evacuated. A sequestrum, the size of an olive, was found

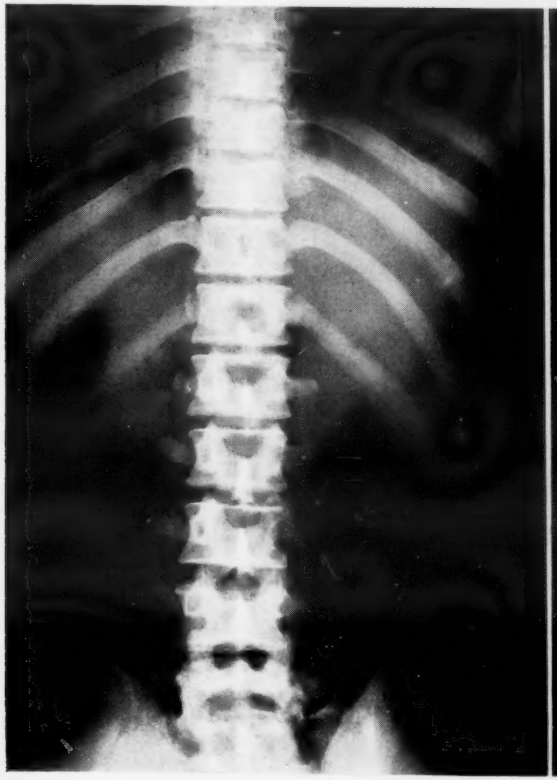

FIG. 1.—Anteroposterior projection: Note the destructive process involving the transverse process and portion of the lateral mass of the third lumbar vertebra.

FIG. 2.—Lateral projection: Note the area of lessened density of the body of the third lumbar vertebra.

FIG. 3.—Two years postoperative: Showing a residual defect of the transverse process. The destructive lesion has been completely arrested and the psoas outline returned to normal.

lying free in the place occupied by the transverse process. This was removed and, subsequently, examined microscopically. The medial wall, formed by the vertebra proper, was thoroughly curetted. The remaining tip of the process and spinal nerves were involved in dense scar tissue. The total removal of the tip seemed impractical because of possible injury to the spinal nerves. This area was, therefore, also curetted as were the remaining walls of the cavity. Following this, an adequate pedicle muscle transplant was developed from the adjacent muscle mass. The free end was firmly fastened in the cavity so that it completely filled the space. The wound was then closed with No. 1 chromic catgut. Black silk was employed to close the skin. The sutures were removed in seven days.

Material removed at the time of operation, including the sequestrum, showed early tubercle formation on pathologic examination. We believe that this adequately substantiates the preoperative clinical and roentgenologic diagnosis.

Subsequent Course.—Convalescence was quite uneventful. No further drainage occurred, and all wounds healed satisfactorily. After an adequate period of bed rest he was started on progressive exercise and finally discharged, September 10, 1937. All wounds, including the cervical sinuses, had been healed for a long time when he left the sanatorium. Since discharge, he has returned to his occupation as a cook. Frequent check-up examinations, including roentgenologic examination (Fig. 3), have all been thoroughly satisfactory. His total weight-gain has been approximately 35 pounds to date.

At the present time the patient is the only living member of a group of four living together prior to his admission. All others have since died of tuberculosis.

COMMENT.—No similar case has been found by us in the literature and, therefore, we assume that we are not only reporting a case of an unusual site for metastatic tuberculous infection, but also have employed a procedure which has given highly satisfactory results which would justify further use with but one modification: We believe that the tip of the transverse process should be completely removed if possible. We thoroughly realize, however, that no definite conclusion can be reached on the basis of a single case.

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BOOKS RECEIVED

THE receipt of books for review is hereby acknowledged. This statement shall be regarded as sufficient acknowledgment of the courtesy of the publishers. Selections will be made for review predicated upon the interests of the readers of the ANNALS OF SURGERY and as space permits.

TEXTBOOK OF GENERAL SURGERY. By Warren H. Cole, M.D., and Robert Elman, M.D. Second Ed. New York: D. Appleton-Century Co., Inc., 1939.

PRATICA CHIRURGICA. By Vittorio Puccinelli, M.D. Bologna, Italy: L. Cappelli, 1939.

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CONTROL OF FEDERAL EXPENDITURES: A DOCUMENTARY HISTORY. Compiled by Fred W. Powell. Washington: The Brookings Institution, 1939.

BOOK REVIEW

SURGICAL TREATMENT OF HAND AND FOREARM INFECTION. By Dr. A. C. J. Brickel, A.B., M.D. Dept. of Anatomy and Surgery, Western Reserve University. 291 pages. 166 text illustrations; 35 plates, including 10 in colors. C. V. Mosby Co., St. Louis, 1939.

For those who are interested in hand infections, here is a comprehensive treatise written by Dr. A. C. J. Brickel. The volume is a thought-producing book divided into seven chapters, so grouped that the busy practitioner can easily find the part dealing with one of his particular cases. The monograph has beautifully colored plates and illustrations which deal with the clinical as well as the surgical anatomy of the hand and forearm. The clinical notes following each description of the compartments of the hand impress one with the importance of properly placed incisions in the hand. The author carefully points out important structures to be avoided, thus reducing the impairment of the function of the hand. The value of the various incisions in the treatment of the individual types of infections is clearly shown by the illustrations.

Following each chapter, the general comments and conclusions will be found to be of aid to the industrial and general surgeon, who is in haste to obtain concrete knowledge concerning an accurate diagnosis of various types of infections, within a short space of time. Other chapters deal with anesthesia, physiotherapy, and medicolegal considerations.

We know that through the use of the hand and arm, man is able to exploit his brain to the fullest extent. The hand is man's second brain, for with it he builds homes, assembles automobiles, builds aeroplanes, writes books, *etc.* The hand is also a supplementary eye, in that, in total darkness, it guides him and gives a sense of security. When one muses and meditates over the dire end-results of hand infections, then it becomes apparent what a useful hand means to a working man.

As an antidote for better results in hand infections, I strongly recommend a careful perusal of this book.

Jerome J. Weiner

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